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

HCV Education & Support:
A Brief History of Hepatitis C

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The management and care of hepatitis C has come a long way in the last decade. While there are still many unanswered questions, we have a much better understanding of hepatitis C transmission, prevention, disease progression and treatment. This factsheet will focus on a brief review of the history of hepatitis C and the major strides made in treating HCV since the identification of the virus.

Ancient History

It is impossible to really know the origins of hepatitis C since there are no stored blood samples to test for the virus that are older than 50 years. However, given the nature of the evolution of all viruses, hepatitis C has probably been around for hundreds of thousands of years or more before evolving into the current strains.

Some experts speculate that since HGV/GBV-C, a close relative of HCV, originated in Old and New World primates, the beginnings of HCV might be traced back to 35 million years ago. However, this is just speculation and it is impossible to corroborate these theories at the present time. On firmer ground is the prediction that the different subtypes of HCV originated approximately 200 years ago and that the six main genotypes of HCV most likely had a common ancestor approximately 400 years ago. However, it has also been pointed out that it is difficult to limit the origin of HCV to such a short period of human history because the virus is found in remote areas all over the world. As well, the virus is mainly spread by direct blood-to-blood contact, making it difficult to spread and evolve rapidly – especially considering that the main transmission routes (blood product use and needle use) have only been in existence for a short period of time.

1957

Scientists discovered the antiviral properties of interferon, a naturally occurring substance in 1957. It was named interferon since it has the ability to 'interfere' with viral replication. Three different types of interferon were identified – alfa, beta and gamma. While it was found that there is only one form of beta and gamma interferon, it was discovered that there were many forms of alfa interferon. Interferon was approved to treat a variety of disorders including hairy cell leukemia, and Kaposi's sarcoma.

1960-1970's

Scientists developed blood tests to identify hepatitis B (1963) and hepatitis A (1973), but many of the blood samples taken for post-transfusion illness tested negative for hepatitis A and hepatitis B.

Given that the mode of transmission (blood transfusion) was the same, scientists classified the unidentified cases as non-A, non-B hepatitis. It is now believed that approximately 90-95% of cases previously classified as non-A, non-B (NA/NB) were actually hepatitis C.

1980-1990's

In the 1980's, investigators from the Centers for Disease Control (headed up by Daniel W. Bradley) and Chiron (Michael Houghton) identified the virus in 1989. In 1990, blood banks began screening blood donors for hepatitis C, but it wasn't until 1992 that a blood test was perfected that effectively eliminated HCV from the

blood transfusion supply. Now, there is less than one per two million transfused units of blood estimated to be tainted with hepatitis C. Prior to the screening of the blood supply for hepatitis C, approximately 300,000 Americans contracted hepatitis C through blood transfusions or blood products.

Treatment Timelines

- 1991 - FDA approves first alfa interferon (Schering's Intron A) to treat hepatitis C.
- 1992 - FDA approves first interferon (Schering-Intron A) to treat hepatitis B.
- 1996 - FDA approves alfa interferon (Roche, now Genentech- Roferon A) to treat hepatitis C.
- 1997 - FDA approves consensus interferon (Amgen-now InterMune-Infergen) to treat hepatitis C.

The general treatment protocol was to inject 3 million units of interferon, three times a week for 48 weeks. Sustained virological response rates (negative viral load 6 months post-treatment) were approximately 9% for genotype 1 and 30% for genotypes 2 and 3.

Treatment Breakthrough

1998

FDA approves Rebetron (Schering's Intron A plus ribavirin) for the treatment of hepatitis C.

Ribavirin is a synthetic nucleoside analogue with a broad spectrum of antiviral activity that was initially developed as a possible treatment for HIV. As it turned out, ribavirin was not effective against HIV, but it was found that it did have antiviral activity against several flaviviruses (a family of viruses that includes hepatitis C), and it was studied as a single agent for the treatment of hepatitis C. In some small studies, ribavirin was found to reduce serum ALT levels, but that it had no effect on the hepatitis C virus. The clinical findings that ribavirin reduced ALT levels led to the studies of combination ribavirin and interferon therapy. It was found that ribavirin when combined with interferon produced a synergy that proved to be a major breakthrough for treating hepatitis C. Ribavirin (in a mist form) is also approved for the treatment of respiratory syncytial virus (RSV) infection in children.

The treatment with combination therapy consists of interferon (Intron A - 3 million units thrice weekly) plus ribavirin (800-1200mg/day). The clinical trials conducted on combination therapy also determined the duration of treatment for genotype 1 as 48 weeks and 24 weeks for genotypes 2 and 3. Overall sustained virological response rates are genotype 1 - 29% (high viral load - 27%); genotypes 2 and 3 - 62% (high viral load - 60%).

A New Era in the Treatment of Hepatitis C

Synthetic interferon is a protein that is broken down rapidly by the body within 12 to 24 hours after injection. The standard protocol for interferon was to inject 3 times a week. But once the synthetic interferon is eliminated by the body, there is no further interferon available to suppress or kill the virus.

Pegylation is a process that attaches polyethylene glycol (a biologically inert compound) strands to the interferon molecule making it less likely to be cleared from the bloodstream. The benefit of increased concentrations of interferon levels over a prolonged period of time is constant suppression of the virus and increased likelihood of a sustained virological response.

2001

Peg-Intron Approved

Peg-Intron (Schering's pegylated interferon alpha-2b) was the first pegylated interferon FDA approved to treat hepatitis C. Peg-Intron is a powder that needs to be reconstituted (with a sterilized solution) before it can be injected. Peg-Intron also needs to be dosed by a person's body weight. Peg-Intron is now available in a "Redipen" for dosing and reconstitution.

The sustained virological response rates for Peg-Intron monotherapy are 14% for genotype 1, and 47% for genotypes 2 and 3.

Peg-Intron plus Rebetol Approved
PEG-Intron plus Rebetol (ribavirin) was also approved in 2001 to treat hepatitis C. Sustained virological response rates are 41% for genotype 1 and 75% for genotypes 2 through 6.

2002

Pegasys Approved
Pegasys (Genentech's pegylated interferon alpha-2a) was approved to treat hepatitis C in 2002. Pegasys comes in a ready made solution (does not need to be reconstituted) and in a dose fixed at 180 micrograms regardless of a person's weight. Pegasys is available in pre-filled syringes.

The sustained virological response (SVR) rate for Pegasys is 28% for genotype 1, and 56% for genotypes 2 and 3. People with advanced fibrosis or compensated cirrhosis (a group that is more difficult to treat) achieved an SVR of 20%. A clinical trial of cirrhotic patients also showed that Pegasys reduced liver inflammation and scarring in treatment responders and, to a lesser degree, in non-responders.

Pegasys plus Copegus Approved
In 2002 Pegasys plus Copegus (Genentech's brand of ribavirin) was also approved for treatment of hepatitis C. Sustained virological response rates are: for genotype 1, 44-51%, and 82% genotypes 2 and 3, while another study found 70% SVR for genotype 2 through 6.

2003

Intron A (interferon) plus Rebetol (ribavirin- available in oral solution) approved for treating pediatric patients with chronic hepatitis C.

2005

HCV Replicated in Test Tube
For the first time, scientists at the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) were able to replicate the hepatitis C virus (genotype 1) in a test tube. This system only represents the end of the viral life cycle, but a very important advance. Another HCV model system is needed to show the beginning stages of the viral life cycle.

Saliva Antibody Test
Israeli scientists developed a saliva-based test for detecting HCV antibodies, which, if confirmed in larger studies, could lead to a new testing mechanism that would be less labor intensive, easier to administer and less expensive thereby making mass testing of hepatitis C a possibility.

2006

Mouse Model
Scientists made dramatic inroads into understanding the various mechanisms of action of the hepatitis C virus and replicated various HCV genotypes in a test tube. Importantly, scientists using a hepatitis C virus cell culture were able to infect a mouse model. Creating a mouse model for the hepatitis C virus has the potential to dramatically increase our knowledge of the hepatitis C virus.

2007

Drugs in Development
In 2007, many new drugs were advanced into development. The leading compound is VX-950 (telaprevir) an HCV protease inhibitor that is being developed by Vertex. There are also many other drugs that are advancing through the clinical trial process and it now appears that a new drug will be added to pegylated interferon plus ribavirin therapy by 2011-2012.

HCV Rapid Test
An HCV rapid test (HCV anti-body test) clinical trial by OraSure was launched in 2007.

2008

OraSure Technologies completed their clinical studies of an HCV rapid test and submitted the data to the FDA for marketing approval. FDA approval is expected in 2010.

Vertex initiated a phase III study of their HCV protease inhibitor, telaprevir, in combination with pegylated interferon plus ribavirin. Schering also initiated a phase III study of their HCV protease inhibitor, boceprevir, in combination with pegylated interferon plus ribavirin.

The phase III studies are expected to be completed in 2009 and the data will be submitted to the FDA for marketing approval in 2010.

The FDA approved the use of Schering's PegIntron plus Rebetol (ribavirin) for the treatment of pediatric patients with compensated chronic hepatitis C. There were a total of 107 pediatric patients who received PegIntron dosed at 60 mcg/m once weekly plus ribavirin dosed at 1.5 mg/kg/day for 24 or 48 weeks based on genotype and baseline viral load. The SVR rates by genotype and treatment duration were 52.8% (all genotype 1 – 48 weeks duration); 93.3% (all genotype 2 – 24 weeks); 100% (genotype 3 low viral load (<600,000 IU/mL); 66.7% (genotype 3 high viral load); and 80% (all genotype 4-48 weeks).

2009

Direct antiviral medications telaprevir and boceprevir (HCV protease inhibitors) finish enrollment in their clinical trials and expect to complete their trials and file for marketing approval late in 2010.

This is the year that the first interferon and ribavirin-free regime of a HCV protease inhibitor (RG7227) and polymerase inhibitor (RG7128) was tested in people with HCV. The study results were encouraging, but it will be many years before a regime without interferon/ribavirin will be available.

It is clear that we have come a long way in a relatively short period of time in the understanding of HCV disease and the therapies used to treat it. Hopefully, in the not too distant future we will have medications that will work for everyone infected with chronic hepatitis C and everyone in the United States will have access to quality medical care.

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HCV Education and Support

- How to Tell Children They Have Hepatitis
- Finding a Hepatitis C Support Group
- Hepatitis C and the Workplace: A Guide for Employers and Coworkers
- Hepatitis C: Disclosure
- Dispelling Myths about HCV
- Testing Positive – Now What?

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

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