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InterMune Relaunches Infergen

By Alan Franciscus
Editor-in-Chief

InterMune, located in the San Francisco Bay Area, is a commercially driven biopharmaceutical company focused on the commercialization, development, and applied research of life-saving therapies for pulmonary disease, infectious disease, and cancer.

Last year, InterMune purchased the rights to market Infergen, (also known as consensus interferon (CIFN), a bioengineered type I interferon alfa from Amgen) and also to have gamma interferon in clinical trials for the prevention of fibrosis. In addition, InterMune plans to develop a pegylated version of consensus interferon, which they anticipate launching in 2005.

InterMune is positioning itself as a formidable competitor in the multi-billion dollar hepatitis C market that will evolve over the next few years.

The hepatitis C market is currently dominated by Schering Plough, which markets Peg Intron (pegylated interferon alpha 2b), Rebetron (interferon alpha 2b plus ribavirin), as well as the sale of ribavirin, to which they have the exclusive marketing rights.

This issue is presently being challenged in the courts, with other companies who want to manufacture a generic form of this drug. Roche is anticipated to enter the arena with Pegasys (pegylated interferon alpha 2a) later in 2002, which many believe will give Schering Plough strong competition, as well as improve the HCV marketplace, since competition generally improves cost and quality.

Many liver disease experts were very supportive of Amgen when they released Infergen and believed that Infergen (consensus interferon) was the best standard interferon. However, Schering Plough's exclusivity rights to ribavirin, which they had bundled in a kit with their own standard interferon, made the combination of Infergen and ribavirin very difficult to

obtain. This angered many patients, advocates, and healthcare providers, because it prevented the use of ribavirin with other possibly more efficacious interferons to treat HCV.

On January 31st, 2002, InterMune, Inc., headquartered in Brisbane, California, announced that the company has re-launched Infergen(R) (Interferon alfacon-1) for the treatment of chronic hepatitis C infection. InterMune recently expanded its sales force to focus on hepatologists and support them in the safe use of Infergen in the treatment of hepatitis C.

"Infergen provides hepatologists with another treatment option for the nearly 50 percent of HCV patients who will either fail or relapse from initial therapy," said W. Scott Harkonen, M.D., President and Chief Executive Officer of InterMune.

Recently, InterMune reported positive interim results from a Phase IV clinical trial comparing the use of Infergen plus ribavirin to the use of interferon alfa-2b plus ribavirin (Rebetron(TM)) to treat chronic hepatitis C. Patients treated with Infergen in combination with ribavirin achieved a sustained virologic response (SVR) of 56% compared with an SVR of 31% in patients treated with Rebetron. Results of the study were presented in November 2001 at the 52nd Annual Meeting of the American Association for the Study of Liver Diseases. Physicians and patients can obtain additional information about Infergen by visiting <http://www.infergen.com/>.

Source: Company Press Release

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Occupational Exposure to Hepatitis C Virus

By Lucinda K. Porter, RN

Occupational exposure is one of the potential risk factors for acquiring hepatitis C virus (HCV) infection. Healthcare workers, fire fighters and public safety officials are examples of professions at increased risk of exposure to bloodborne pathogens.

In an article in *The New England Journal of Medicine* (1999; 341:556), Miriam Alter presented data on the risk of transmission by a single needle stick incident to a susceptible healthcare worker. The approximate risk for hepatitis B is 30%, hepatitis C 3% and HIV 0.3%. In October of 1998, the Centers for Disease Control (CDC) Morbidity and Mortality Weekly Report (MMWR), addressed issues relating to hepatitis C. The report titled "Recommendations for Control and Prevention of Hepatitis C Virus Infection and HCV-Related Chronic Disease," provided valuable guidelines for the management of HCV.

The report acknowledged an increased risk to certain occupations but did not recommend routine HCV screening unless there was a specific exposure. The policies for post-exposure management vary with individual institutions. Immunglobulin and anti-viral treatment were not recommended for prophylaxis following exposure to HCV. The CDC reported that little was known about the use of antiviral therapy for acute HCV infection, but postulated that early intervention might be beneficial.

At the time of this report, there were limited data and therefore the CDC was unable to make a standard guideline. The CDC updated its recommendations in the June 29, 2001 issue of MMWR. Using a "needle stick" as an example, these recommendations include the following:

Check the source of the needle stick contaminant for HCV RNA (evidence of virus)

Obtain a baseline HCV antibody and alanine aminotransferase (ALT) level for the person who had the needle stick injury

Perform follow-up HCV antibody and ALT level at 4-6 weeks or as late as 4-6 months

Prophylaxis not needed

No work restrictions



HealthWise

Unfortunately, when the CDC made their recommendations in the summer, they had no idea that results of an important study would be released in the November 15, 2001 issue of the *New England Journal of Medicine*. A research team led by Dr. Elmar Jaeckel of the Hanover Medical University of Hanover, Germany conducted this study. A report on this research was written by Alan Franciscus and appeared in the November 2001 HCV Advocate. The following are excerpts from his article.

"The German team studied 44 patients (between 18 to 65 years old) from 24 medical centers who contracted HCV to study the effectiveness of treating newly acquired HCV infection with interferon monotherapy. The selection criteria for this trial required the participants to be HCV RNA positive to a polymerase-chain-reaction (PCR) assay and have elevated serum ALT levels of more than 350. The source of exposure to HCV was determined to be injection drug use (9 people), needle-stick injury (14), medical procedure (7), sexual contact (10), and unknown or unclear source (4). The distribution by genotype was 1 (27 people), genotype 2 or 3 (12), genotype 4 (0) and unknown genotype (5). All subjects were each treated with 5 million units (MU) of interferon alfa-2b (Intron A) for the first four weeks, followed by 5 MU three times a week for another 20 weeks. Forty-three patients completed the study. Intent to treat results reported that 95% of patients cleared the hepatitis C virus (42 patients out of 44 patients - one patient dropped out at 12 weeks due to adverse events). Treatment (patients that completed therapy) results reported 98% of patients cleared the hepatitis C virus (42 patients out of 43 patients that completed the study)." Alan concludes his article with a well-reasoned editorial that prompts the reader to look further into the issue. "It is clear that the results of this study strongly suggest that HCV can be eliminated if treatment is initiated soon after exposure.

It is important to look at another viewpoint on this. It is known that 20-25% of patients will spontaneously clear the HCV virus and not go onto chronic infection.

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The Liver and How It Works

By Liz Highleyman
Contributing Editor

The liver, the largest internal organ, is responsible for many vital bodily functions. It plays an important role in metabolism and processes almost everything a person ingests, breathes, or absorbs through the skin. Hepatitis is a general name for inflammation of the liver. As liver damage progresses, the organ may no longer be able to carry out its normal functions, leading to a variety of symptoms and associated conditions.

Liver Anatomy

The liver weighs approximately three pounds (in the adult male) and is about the size of a football. It is located behind the ribcage on the upper right side of the abdomen. The liver has the ability to regenerate its own tissue; as much as three-quarters of the liver can be lost and the organ can grow back within several weeks. The liver is divided into four lobes; these are in turn made up of multiple lobules, which contain hepatocytes, or working liver cells.

Functions of the Liver

The liver is responsible for over 500 bodily functions. It plays an important role in the digestion and processing of food. About 90% of the body's nutrients pass through the liver from the intestines. The liver converts food into energy and stores several nutrients for later use. It also stores iron and plays a role in converting iron into heme, a component of hemoglobin (the oxygen-carrying molecule in red blood cells). Liver cells produce bile, a greenish-yellow fluid that aids the digestion of fats and the absorption of fat-soluble nutrients. By-products from the metabolism of drugs and toxic substances are carried in the bile and excreted from the body. The liver also converts heme into bilirubin; when the liver is damaged, bilirubin may build up in the blood and cause jaundice (yellowing of the skin and whites of the eyes).

The liver carries out many metabolic functions. It regulates the production, storage, and release of sugar, fats, and cholesterol. When food is eaten, the liver converts glucose (blood sugar) into glycogen, which is stored for later use. When energy is needed, the liver converts glycogen back into glucose in a

process called gluconeogenesis.

The liver regulates the storage of fats by converting amino acids from digested food into fatty acids such as triglycerides; when the body does not have enough sugar, the liver converts fatty acids into ketones, which the muscles use for fuel. The liver synthesizes several important proteins, including enzymes, hormones, clotting factors, and immune factors. Liver enzymes called aminotransferases (ALT and AST) break down amino acids from digested food and rebuild them into new proteins needed by the body. When the liver is damaged, these enzymes can build up to high levels in the blood; it is these enzymes that are measured in liver function tests. Other proteins synthesized by the liver include alkaline phosphatase and gamma-glutamyl transferase (GGT). Several proteins synthesized by the liver are necessary for proper blood functioning; these include binding proteins and albumin, which helps maintain proper blood volume. Clotting factors produced by the liver include fibrinogen, prothrombin (Factor II), and Factor VII.

The liver also acts as a filter to remove pathogens and toxins from the blood. It processes almost everything a person eats, breathes, or absorbs through the skin. The liver detoxifies harmful substances including alcohol, drugs, solvents, pesticides, and heavy metals. It also processes and excretes toxic byproducts of normal metabolism (such as ammonia) and excess hormones (such as estrogen). Many drugs can cause liver damage if taken in high doses or for prolonged periods. A damaged liver may not be able to break down and excrete drugs efficiently, potentially leading to dangerously high blood levels and increased side effects.

Liver Damage

Viruses (such as hepatitis A, B, and C), heavy alcohol use, and other factors can cause liver inflammation and damage. Given how many vital functions the liver performs, it is not surprising that liver injury can have an affect on almost all body systems, including the digestive, endocrine, cardiovascular, and immune systems. As the liver sustains damage, normal liver tissue becomes fibrous (fibrosis), fatty (steatosis), and scarred (cirrhosis). If the liver becomes

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too damaged, it can no longer carry out its normal activities. In compensated cirrhosis, the liver is scarred but can still function relatively normally. In decompensated cirrhosis, however, the liver has sustained so much damage that it cannot function properly. Scar tissue may block the normal flow of blood through the liver, leading to portal hypertension (high blood pressure) and the development of bleeding varices (stretched and weakened blood vessels) in the esophagus and stomach. People with severe liver damage may also develop ascites (fluid accumulation in the abdomen) and edema (swelling, especially in the legs and ankles). If the liver is unable to filter out toxins and metabolic byproducts such as ammonia, these substances can build up in the blood and cause impaired mental functioning (hepatic encephalopathy), itching (pruritis), and in severe cases, coma.

Liver Health

People can take several measures to keep their liver healthy, whether or not they have an existing liver disease such as HCV. Eat a healthy, well-balanced diet that is low in fat, cholesterol, and sodium, and high in complex carbohydrates. Many experts recommend that people with hepatitis should avoid raw or undercooked shellfish, preserved foods, fruits and vegetables treated with pesticides, caffeine, chocolate, and high doses of vitamin A, vitamin D, iron, and niacin. The National Institutes of Health recommends that people should drink no more than one alcoholic beverage per day, and many experts recommend that people with HCV should not drink alcohol at all. Be

cautious when using drugs, including prescription and over-the-counter medications, recreational drugs, and herbal remedies. Avoid exposure to toxins such as solvents, paint thinners, and pesticides; if it is necessary to use such chemicals, work in a well ventilated area, cover the skin, and wear gloves and a protective face mask. Finally, there are vaccines to prevent hepatitis A and hepatitis B, although there is currently no hepatitis C vaccine.

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Kava Warning

Products containing the herbal extract kava-kava (or simply kava) have been implicated in 25 reports of liver toxicity in Germany and Switzerland, one of which resulted in death. Based on these reports, the regulatory authority in Switzerland has prohibited the sale of products containing the popular kava extract.

In addition, German authorities issued a proposal to remove all kava-containing products from the market. Kava is a popular herb commonly used to treat anxiety, nervousness, pain, muscle tension, and sleep problems. Since kava is an herb, it is not subject to regulation by the United States Food and Drug Administration (FDA).

However, the FDA is asking medical providers to report such cases to: United States 1-800-332-1088
Canada 1-866-234-2345

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Hepatitis C Support Project - A Tides Center Project

Healthwise

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Keeping that in mind, would it be appropriate to subject all acute cases of HCV to the harshness of interferon therapy?

To get a clearer understanding of how to manage the acute cases of HCV, a comparison would need to be done looking at the difference in Sustained Virological Response (SVR) in patients treated immediately after documented HCV exposure or at 6 months when chronic HCV infection can be confirmed. If this study yielded equally effective results, then the 20-25% of patients that usually spontaneously clear the virus after acute infection would not have to be exposed to interferon.

One of the most interesting aspects of this study is the method that participants were recruited. Over 7000 brochures were distributed to hospitals, outpatient clinics, private practices, patient-advocacy groups, and the German Central Registry of Work-Related Accidents.

If these results can be replicated and documented to be superior than waiting to treat chronic disease then this speaks strongly to federal, state and local health departments to step up efforts to increase awareness, testing and counseling for HCV to help identify newly infected HCV individuals.

Such an approach may also prove to be cost-effective in managing HCV, as acute HCV treatment

did not include ribavirin, which is an expensive drug. In addition, this approach should decrease associated costs of managing chronic HCV such as liver biopsy, laboratory tests and lost work productivity to name a few.” The German study has provided valuable information to facilitate the management of acute HCV infection.

This study is bound to influence the recommendations in the management of acute HCV infection that are expected from the National Institutes of Health (NIH) consensus conference later this year. In the meantime, if you are in an increased risk occupation, find out the post-exposure management policy of your employer. Ask when the procedures were last reviewed and do they take into consideration the latest research.

Remember the best way to protect oneself is by using universal precautions. Review these precautions regularly and do not veer from them. Although needle sticks and other forms of exposures do occur, the adage about an ounce of prevention applies aptly in this case. For more information about bloodborne pathogens, visit www.osha.gov

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Lucinda K. Porter, RN is a research nurse and patient educator at Stanford in the area of hepatology. She co-facilitates a support group and is active in many aspects of hepatitis C education. In addition to being HCV positive, she has a life which include her husband and teenaged daughter.

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Steatosis: Does it Accelerate the Progression of Liver Damage in People with Chronic Hepatitis C?

By Alan Franciscus
Editor-in-Chief

Chronic hepatitis C virus (HCV) infection may result in a broad clinical and prognostic (predictive) range of severity. It may lead to liver disease progression ranging from minimal to severe hepatitis to cirrhosis (scarring) to hepatocellular carcinoma (liver cancer) in a minority of people. The factors implicated in the progression of liver disease are not well established.

Hepatic steatosis (fat accumulation in the liver), bile duct damage, and portal lymphoid aggregation/follicles are histological characteristics frequently seen in patients with chronic HCV infection.

According to reports from North America and Europe, the incidence of hepatic steatosis ranges from 31% to 72% in patients with chronic hepatitis C. Hepatic steatosis is also frequently seen in patients with alcoholism, diabetes mellitus, obesity, and hyperlipidemia (high blood fat levels), and in patients who have taken medications such as tetracycline and steroids.

Until recently it has not been established whether steatosis may play a role in the development of fibrosis (the development of fibrous tissue) in chronic hepatitis C patients. It also has not been known whether steatosis may be a direct consequence of HCV infection, secondary to host factors, or both.

Recent data suggests that HCV, through its core protein, may directly cause steatosis, and that hepatic steatosis may be linked with body mass index (BMI, a measure of body fat) and with liver fibrosis in chronic hepatitis C patients. In vitro (laboratory) and in vivo (animal and human) studies have shown that HCV core protein expression in either cell culture systems or in transgenic mice directly leads to the development of hepatic steatosis.

Other factors in chronic hepatitis C patients with hepatic steatosis, including serum HCV RNA viral load, HCV genotype, and host factors such as obesity and serum triglyceride levels, until recently

have not been well studied.

The results of a study published by Luigi Adinolfi and colleagues in the June 2001 issue of *Hepatology* indicated that steatosis - and particularly higher grades of steatosis - are of clinical relevance because they play an important role in accelerating the progression of chronic hepatitis C.

Patients with significant steatosis (i.e., greater than 30%) showed a higher hepatic fibrosis score than those with lower grades (less than 30%) or without steatosis. In addition, higher necroinflammatory activity (tissue inflammation and death) and higher serum levels of aminotransferases and γ -GT were observed in patients with steatosis.

These findings were independent of age, gender, viral factors, and iron deposition. Therefore, chronic hepatitis C patients with a high grade of steatosis may represent a group at risk of more rapid progression to cirrhosis. Patients with grade 3 or 4 steatosis showed a significantly higher amount of fibrosis and a fibrosis progression rate twice as high as those with grade 0-2 steatosis.

This study also showed that patients infected with genotype 3a HCV had the highest prevalence of steatosis and displayed a degree of liver fibrosis comparable to that of those infected with genotype 1a, despite a significantly shorter duration of disease. It was also shown that chronic hepatitis C patients with moderate steatosis showed more necroinflammatory activity and fibrosis than those with mild steatosis. Additionally, the study showed that males had a higher prevalence of grade 3-4 steatosis than females. This may in part explain the greater progression of liver disease reported in men.

A study by Luke Hourigan and colleagues published in the April 1999 issue of *Hepatology* showed a relationship between steatosis, fibrosis, and BMI in patients with chronic hepatitis C, suggesting that obesity plays a role in the pathogenesis (the origin and development) of steatosis.

The results of the Adinolfi study described above confirmed what many other investigators had hypoth-

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esized: that visceral obesity (fat surrounding the abdominal organs), but not total fat mass, was the actual predictor of steatosis. Furthermore, visceral fat is a predictor of hyperinsulinemia (high insulin levels) and peripheral insulin resistance. It has also been shown that in addition to visceral obesity, viral factors play an important role in the development of steatosis. Adolfini's study showed that the incidence of steatosis in patients with various HCV genotypes was significantly different. Patients infected with genotype 3a HCV had the highest prevalence of steatosis, followed by those with genotype 2a/c infection, and lastly by those with genotype 1 infection.

In addition, in patients with genotype 3a infection, steatosis was closely related to level of HCV viremia (virus in the blood), which reflects intrahepatic viral replication; this association was independent of age, obesity, iron deposition, alcohol intake, and drug use. The association between liver steatosis and HCV genotype 3 suggests that specific viral sequences uncharacteristic of this viral strain may be responsible for the steatotic phenotype.

Furthermore, a correlation has been reported between genomic and negative-strand HCV RNA titer in the liver and severity of steatosis, and response to antiviral treatment is associated with the disappearance of fatty accumulation from hepatocytes (liver cells). Although these data seem to emphasize the role of HCV in inducing fat accumulation, some objections can be raised.

Patients with genotype 3 HCV often have a past history of intravenous drug use, and therefore exposure to blood-borne infections, which may be the real offender in provoking liver steatosis, with HCV being a simple "bystander." Injection drug users may also present with a history of alcohol abuse, which may be an additional factor in inducing steatosis.

Despite these caveats, the Adinolfi study showed no difference in hepatic iron storage or alcohol intake between patients infected with genotype 3a and those with genotype 1a who were comparable in age and history of drug use. In summary, the data available to date indicate that obesity, diet, diabetes,

hyperinsulinemia, alcohol consumption, and HCV virus factors play a role in the development of steatosis. In particular, visceral obesity and genotype 3 HCV are clearly associated with steatosis, with the latter being the major determinant of fibrosis progression.

It is important to note that genotype 3a has only recently been introduced into the United States and tends to affect young people, mainly injection drug users; it is expected that in the future an increasing number of patients with cirrhosis will come from this population.

Additionally, the data suggests that alcohol exerts a synergistic effect with steatosis in accelerating the progression of liver disease, even at low consumption levels (10 to 30 g/day). In chronic hepatitis C infection, steatosis is an important co-factor in accelerating the development of hepatic fibrosis and increasing necroinflammatory activity, and both host and viral factors play a role in the pathogenesis of steatosis in chronic hepatitis C patients.

Managing steatosis could potentially slow the progression of chronic hepatitis C, which would be of particular importance for patients who are non-responders to current antiviral therapies. Even though steatosis is correlated with many factors, restoration of normal weight in subjects with visceral obesity will likely have significant clinical importance in slowing the progression of liver disease in patients with chronic hepatitis C.

In addition, therapeutic strategies that significantly reduce HCV RNA levels and/or steatosis might be effective in controlling or slowing HCV-related liver damage.

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