This was the title of a talk that I attended in the Summer of 2011. It may sound cliché, but when it comes to the treatment of a virus for which there has been little progress, until recently, it speaks volumes. On May 13, 2011, the Food and Drug Administration (FDA) approved boceprevir (Victrelis®) for the treatment of chronic hepatitis C virus (HCV), in certain individuals with genotype 1. Ten days later on May 23, 2011, the FDA approved telaprevir (Incivek®), a second HCV protease inhibitor. With those two announcements, the treatment of HCV has forever changed; the first change since 1998 when “double therapy” was approved as standard of care (SOC) for HCV infections. These two protease inhibitors bring with them the potential to cure persons with Genotype 1 HCV, the most common genotype in the United States, and until now, the Genotype with the poorest cure rates. With continued advances in HCV therapeutic research, there is hope that one day all persons living with HCV can be cured of this chronic infection.

Epidemiology

HCV infection is the most common chronic blood borne infection in the United States1, accounting for up to two-thirds of newly diagnosed cases of chronic liver disease2. As of 2006, the estimated burden of HCV was 3.2 million persons (prevalence of 1.3%)1. There are several modes of transmission for HCV (See Table 1), however a majority of persons living with HCV, contracted it through the usage of Intravenous Drug Use (IVDU). Until 1992, when Universal Blood Screening was initiated for HCV, blood transfusions played a major role in HCV transmission. Although IVDU drives most of the prevalent HCV infection, other risk factors, including sharing of razor blades and tattoo equipment, health care related exposures and sexual intercourse, particularly in those infected with Human Immunodeficiency Virus (HIV), also play roles in HCV transmission (See Table 1). In an effort to improve detection of those living with HCV, the CDC on May 18, 2012, announced new recommendations for testing all persons born between 1945 and 1965 for Hepatitis C3. This screening recommendation is expected to identify the nearly 80% of persons living with HCV that are unaware of their infection. The recommendation will also reduce the burden primary care and specialty providers, present experience when faced with the task of discussing uncomfortable risk factors with patients in a short clinic encounter time.

Table 1 – HCV Transmission Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection drug users with a history of IVDU</td>
</tr>
<tr>
<td>Individuals Infected with HIV</td>
</tr>
<tr>
<td>Individuals with hemophilia</td>
</tr>
<tr>
<td>Recipients of clotting factors or other blood products before 1987</td>
</tr>
<tr>
<td>Hemodialysis patients</td>
</tr>
<tr>
<td>Individuals with elevated liver enzyme levels</td>
</tr>
<tr>
<td>Recipients of solid organ transplants before 1992</td>
</tr>
<tr>
<td>Recipients of blood transfusions before 1992</td>
</tr>
<tr>
<td>Children born to HCV-positive mothers</td>
</tr>
<tr>
<td>Individuals with any known potential exposures via HCV-positive blood donors, organ donors or occupational exposure</td>
</tr>
<tr>
<td>Sexual partners of HCV-infected individuals</td>
</tr>
</tbody>
</table>

Table adapted from AASLD Website using Hepatology and MMWR4,5.

After acute HCV infection, about 15%–25% of persons clear the virus from their bodies without treatment. This group may represent a patient panel seen in practice with positive HCV antibody and negative HCV viral load (HCV RNA PCR). This leaves 75%–85% of patients who will evolve to a chronic HCV infection. Of these, 60–70% will go on to develop chronic liver disease, with another 5–20% developing liver cirrhosis (usually over 20–30 years), and 1–5% will eventually die from the consequences of chronic infection, liver cancer or cirrhosis.

It is important to remember that 60–70% of patients with acute HCV infection are asymptomatic. Since patients living with chronic HCV have no symptoms until the virus has damaged the liver, this obviates a historically important part of medicine – the clinical history. Instead of being able to screen patients based on poignant clinical interviews and judgment, lab tests are key to making a diagnosis of HCV. Previous studies have shown that unless a high index of clinical suspicion is used to identify HCV infected patients, most will go undetected despite repeated interactions with several sectors of the health sector6.5. Due to the stealthy nature of HCV infection during the years of hepatic destruction, the Institute of Medicine (IOM) estimates that approximately 75% of HCV patients are unaware of their infection6.

Growing Burden

Two-thirds of the persons with HCV infection are “Baby Boomers,” or persons born between 1946 and 19646,7; these persons will be between 47 and 67 in 2012. With the death rate from HCV infection expected to triple over the next two decades, the burden to society due to HCV is becoming significantly great5. The new therapies bring a cost concern to the healthcare system, particularly to patients living with HCV. Liu and colleagues, in a recent study point to the fact that using newly established triple therapy, even in patients with advanced liver disease is cost-effective.1 Therefore, Continued on page 11
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(Continued)

to reduce the long term effects to persons living with HCV, as well as minimizing the strain to our already overburdened infrastructure, it is imperative that healthcare policy makers focus on investing in strategies to identify and treat patients living with HCV.

El Paso Focus
According to the Census Bureau, Hispanics are the fastest growing and the largest minority group in the U.S. El Paso, based on 2010 Census figures, is 81% Hispanic. Although previous National Health and Nutrition Examination Survey (NHANES III), showed Mexican-Americans had a higher anti-HCV positivity rate than Caucasians (2.1%, 95% CI: 1.7-2.6) and were more likely to be viremic (73.6%, 95% CI: 66.8-81.2%), after adjusting race and ethnicity they were found not to be independently associated with HCV infection2. Across the nation, the prevalence of HCV is significantly higher in men compared to women, with Mexican Americans having a prevalence of 1.3% (compared to 1.5% for Non-Hispanic whites). Over the last 20 years the demographics of HCV infection have changed, with the peak age-specific prevalence moving from infected patients in the 30 to 39 age range, to the 40 to 49 age range2. With these changing demographics, nationally, and particularly in El Paso, we can expect to see a large present day population of elderly Mexican Americans with HCV infection.

The alarming fact that a majority of patients living with HCV are asymptomatic creates a looming health challenge to health care providers in El Paso. One way to identify patients living with Chronic HCV is to do a one-time antibody test of all individuals born between 1945 and 1965. This has recently been shown to be cost-effective3, and may provide primary care providers an efficient way to identify and screen for chronic HCV. In the following sections, we will attempt to outline the basics of Hepatitis C therapy, and some of the referral options available to providers in El Paso.

HEPATITIS C MEDICATIONS

Ribavirin
Ribavirin is an antiviral nucleoside analogue medication that interferes with viral DNA and RNA replication. There are several formulations of ribavirin available (Copegus, Rebetol, Ribax-Pak, Ribalex, Ribavirin) some requiring refrigeration for storage. Ribavirin is never used as monotherapy for hepatitis C (HCV), although it has other medical indications, including treatment of RSV, Vachaphia and hemorrhagic fever. Dosing and therapy duration are weight, genotype, and viral response dependent.

Ribavirin’s primary toxicity is hemolytic anemia; this usually develops after 2 weeks of therapy, is dependent on the dosage, and is reversible once the medication is discontinued. It is common for Ribavirin to be dose-adjusted during therapy to reduce the degree of anemia patients may develop.

Ribavirin is teratogenic, and two methods of contraception are required in patients currently undergoing HCV treatment and for 6 months after completion. Concomitant use of ribavirin with didanosine should be avoided due to increased risk for toxicity including hepatotoxicity and pancreatitis. Other important drug drug interactions to monitor include azithromycin, nucleoside reverse transcriptase inhibitors, zidovudine and the influenza virus vaccine.

Weekly cost14,15
Rebetol® 200 mg capsule (1,200 mg/day):
$387.16 ($0.92/capsule)
Ribavirin® 200 mg capsule (1,200 mg/day):
$189.84 ($0.45/capsule)

Pegylated Interferon Alfa
Interferons are proteins produced by cells in the body that fight viral infections. Interferons attach to cells setting off a cascade of activity dependent which allows the body to recover of a virus. There are three types of interferon identified: alpha, beta, and gamma. Interferon-alpha was initially used to treat hepatitis requiring daily to three times a week subcutaneous injections. Modification of the interferons by Pegylation (PEG) extends the duration interferon remains in the body and decreases the frequency of injections from daily to weekly. There are two peg-interferon 2a products available, Pegasys and Peg-Intron. Until recently, all genotypes of HCV were treated with a combination of peg-interferon alpha plus ribavirin.

While Peg-Intron can be used in children as young as 3 years old, Pegasys is only indicated in children 5 years or older. Dosing is weight-based and treatment duration is determined by genotype and virological response at specific treatment time points.

Peg-interferon’s adverse drug reaction (ADR) profile is extensive, ranging from flu-like symptoms, to gastrointestinal intolerance. Of note are the neuropsychiatric ADRs, which are very depression and suicidality. It may also lead to bone marrow suppression, potentiation or aggravating the effects of ribavirin. Ironically, it was also cause hepatitis. As with ribavirin, peg-interferon is teratogenic, and female patients must have a pregnancy test prior to starting therapy, with regular testing during treatment; they must also be on two forms of contraception.

Weekly cost14,16
Pegasys® 180 mcg/vial (180 mcg/week):
$700.00 ($700/vial)
 Peg-Intron® 120 mcg/vial (120 mcg/week):
$640.99 ($640.99/vial)

Protease Inhibitors
Up until last year, the chances of successful therapy using Ribavirin and pegylated interferon, for persons living with HCV Genotype 1, were quite disappointing; averaging anywhere from 20-60%, based on race, degree of liver disease, and several other factors. In May of 2011, the FDA approved two protease inhibitors (PI) for use in combination with standard therapy which can, in certain circumstances, increase the chance of therapy success to rates near 90%. Protease inhibitors function by blocking an enzyme that HCV needs in order to replicate itself. There are currently two PI’s approved by the FDA for the treatment of chronic hepatitis C - boceprevir (Victrelis®) and telaprevir (Incivek®).

Treatment regimens differ depending on which PI is used. A boceprevir-based regimen requires a ‘lead in’ period of peg-interferon and ribavirin for 4 weeks, followed by a combination of boceprevir, peg-interferon and ribavirin for another 24 weeks to 32

Continued on page 12
weeks (with subsequent peg-interferon and ribavirin for an additional 12 weeks) depending on viral response. With telaprevir, treatment is initiated with the three medications and continued for 12 weeks, after which treatment is simplified to interferon and ribavirin alone for 12 weeks or 36 weeks depending on viral response. Both PIs are also approved for the treatment of partial and null responders, as well as cirrhotic patients.

The pill burden with these new therapies is fairly daunting. Boceprevir comes in 200 mg capsules, and is taken as 4 capsules three times daily (12 capsules daily). Telaprevir, on the other hand comes in 375 mg tablets, and is dosed as 2 tablets three times a day (6 tablets daily) with a meal containing at least 30 grams of fat (needed for appropriate absorption).

Both PIs have multiple drug-drug interactions due to their inhibition of the CYP3A4 system. Several drug studies are in the works to identify and characterize the various interactions. A good guide to HCV PI interactions is - http://www.hep-druginteractions.org/; however, many interactions are being discovered based on clinical experience. Several clinics around the country are utilizing clinical pharmacists to assist with the myriad ADRs, and drug-drug interactions. Boceprevir’s most concerning ADR is anemia necessitating CBC monitoring at periodic intervals during therapy. It may also lead to dysgeusia by causing a metallic taste in the mouth. Anemia and mild skin reactions which may become severe are the most concerning ADRs reported with telaprevir. Telaprevir also has a uniquely burdensome ADR of anorectal pruritis, which can be controlled by steroid anti-itch creams.

**Cost of Combination Therapy**

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Genotypes 2, 3</th>
<th>Genotypes 1, 4</th>
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<tbody>
<tr>
<td>PEG/RBV*</td>
<td>Total: 24 weeks $16,122</td>
<td>Total: 48 weeks $32,245</td>
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*Pegasys

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Early Response</th>
<th>Slow Response</th>
<th>Cirrhosis</th>
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<tr>
<td>Boceprevir + PEG/RBV</td>
<td>Total: 28 weeks $26,400</td>
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<td>Total: 48 weeks $48,400</td>
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<td>24 weeks $18,827</td>
<td>48 weeks $32,257</td>
<td>48 weeks $32,257</td>
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<td></td>
<td>$45,227</td>
<td>$67,475</td>
<td>$80,675</td>
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</table>

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Early Response</th>
<th>Slow Response</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir + PEG/RBV</td>
<td>Total: 24 weeks $149,200</td>
<td>Total: 48 weeks $162,245</td>
<td>Total: 48 weeks $181,445</td>
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<tr>
<td></td>
<td>12 weeks $116,125</td>
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<tr>
<td></td>
<td>$65,522</td>
<td>$81,445</td>
<td>$81,445</td>
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</tbody>
</table>

*Pegasys; Peginterferon

**Weekly cost**

- Boceprevir 200 mg capsule (2,400 mg/day): $1,290 ($15.33/capsule)
- Telaprevir 375 mg tablet (2,250 mg/day): $4,100 ($97.62/capsule)

**Role/Importance of Clinical Pharmacist Support in HCV Treatment Management**

Medication adherence and management of ADRs are key to successful treating HCV. Unfortunately, data shows that at least one medication-related ADR occurs in approximately 75% of patients on chronic HCV treatment, which may compromise patient adherence to medication. Trained clinical pharmacists are at an ideal position to treat HCV as primary care providers due to their accessibility and ability to educate patients regarding treatment, ADRs, drug interactions and about the importance of adherence to medications and a healthy lifestyle. More importantly, clinical pharmacists can monitor and manage ADRs in a timely manner.

The goal of ADR management is to improve quality of life and patient adherence. Mild to moderate toxicities of peg-interferon include flu-like symptoms that can be managed with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). More severe ADRs include bone marrow suppression such as neutropenia or thrombocytopenia, cognitive effects and thyroiditis. Bone marrow suppression can be treated effectively by temporarily or permanently reducing treatment dose. Granulocyte colony-stimulating factors (G-CSF) have been used, but supporting evidence is controversial. Cognitive effects such as depression or irritability can be treated with antidepressants, commonly selective serotonin reuptake inhibitors (SSRIs), and anxiolytics.

Clinical pharmacists have been participating in multidisciplinary teams and leading chronic disease state management clinics successfully for years now. Moreover, pharmacist-managed HCV clinics have proven to be safe and effective according to a study published by the U.S. Department of Veterans Affairs. Although
"The Future is Now!" (Continued)

studies comparing pharmacist and physician-managed treatment are still lacking, pharmacist involvement in HCV clinics is expected to grow over the next few years, especially as data and awareness becomes more readily available.

Medications in the Pipeline
The addition of boceprevir or telaprevir to combination therapy with peg-interferon and ribavirin has shown significant improvement in sustained virologic response (SVR) rates, which can be defined as continued undetectable viral load 6 months after the end of treatment. However, the high pill burden and significant ADRs from these medication regimens may continue to make these treatment options intolerable for some patients and may ultimately become a better option for null responders, partial responders, or relapsers.

Due to a more thorough understanding of HCV replication mechanisms, there are currently a multitude of direct-acting antivirals (DAA) and immune modifiers under clinical investigation in Phase I, II and III trials for the treatment of HCV. Hopes are high that these novel drugs and drug combinations will make the treatment of chronic HCV more successful, more tolerable, and less arduous by reducing pill burden. For a complete list of drugs currently in the pipeline: http://www.hcvadvocate.org/hepatitis/hepc/HCVDugs.html

El Paso Testing and Treatment Options
There are a number of free testing centers throughout El Paso (http://www.hepcchallenge.org/map/usa_county/?state=texas&county=El%20Paso). With funding from the Texas Department of State Health Services (DSHS), the City of El Paso Department of Public Health has recently embarked on a project that offers free HCV testing targeted towards IV DU. The initiative, which began in October of 2011, is staffed by the City’s HIV prevention staff. These staff are actively educating the community about HCV, providing preventive tools and free testing to those at high risk. Clients testing positive are referred to Texas Tech Hepatitis Care Clinic for a medical evaluation and treatment, as needed.

For providers with HCV positive patients, it is recommended that they be seen by a specialist in HCV treatment. This presently runs the gamut from Gastroenterologists/Hepatologists (TTUHSC and several private offices) to Infectious Diseases specialists (TTUHSC, VA and several private offices), and HCV specialized Pharmacists (LaFe). As in the early days of HIV therapeutics, HCV treatment medications have several ADRs, and a coordinated treatment team involving a provider, pharmacist, and patient education specialist is recommended.

TTUHSC role in HIV & HCV
TTUHSC has recently created a Hepatitis Care Clinic (HCC) as collaboration between Roberta Romero, FNP, an expert patient advocate/educator in HCV, Richard Guerrero MD, a Hepatologist, and Ogechukwu Atunzie MD, an Infectious Disease specialist. This unique interface of specialties provides patients seeking HCV treatment, the highest degree of expert care in El Paso, in an environment where several specialists working in HCV can combine to give them standard care therapies.

In collaboration with the El Paso City Health Department, DSHS, Aliviane and a local specialty pharmacy, Ms. Romero spearheaded an initiative to create a Hepatitis C Support Group. This group meets every third Thursday of the month at Texas Tech. Clients or providers interested can contact Roberta Romero at 915-545-6626, ext. 306.

In an attempt to coordinate testing and treatment alternatives for patients living with HCV in El Paso, the Hepatitis Care Clinic is in the process of creating a HCV Registry. One of the academic thrusts of this HCV Registry is to give El Pasoans access to current and future cutting edge therapies for HCV. This registry will also create a repository of Hispanic-specific hepatitis information for researchers, medical students and area/regional medical professionals, which will drive further collaborative research and treatment concepts targeted to our unique environment.

References
12. The Website Services & Coordination Staff UCB, Census Bureau.


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