

The Big 3 at AASLD: *Drugs in Development*



Alan Franciscus, Editor-in-Chief

The 2007 American Association for the Study of Liver Diseases (AASLD) conference included data on a variety of new medications to treat hepatitis C. This is a very exciting era in the understanding of the hepatitis C virus and in the discovery of new medications that will be used in combination with pegylated interferon plus ribavirin to increase the effectiveness of treatment. This year I am concentrating on the data from three drugs in development that I believe provided the most important news stories from this year's conference.

The top news story is about telaprevir (VX-950) followed by Albuferon and R1626. I am also providing my own analyses based on what I have learned while attending the poster sessions, oral presentations and discussing the results with various HCV advocates and medical providers.

TELAPREVIR

The HCV protease inhibitor that is furthest along in development is telaprevir (VX-950). At this year's AASLD conference a couple of posters and presentations were released. The most exciting were the results from two Phase II studies (**PROVE 1** and **PROVE 2**). The PROVE studies included HCV genotype 1 patients who had not

been previously treated (treatment naïve).

PROVE 1:

A total of 250 patients in the United States were enrolled in this Phase 2 study. The study participants were non-cirrhotic, treatment naïve genotype 1. The patient characteristics were well matched across the treatment arms.

The study participants were randomized into 4 different groups:

- **Arm A:** 75 patients treated with Pegasys plus ribavirin for 48 weeks (control arm).
- **Arm B:** 79 patients treated with telaprevir plus Pegasys/ribavirin for 12 weeks, then treated for an additional 36 weeks with Pegasys plus ribavirin.
- **Arm C:** 79 patients treated with telaprevir plus Pegasys/ribavirin for 12 weeks followed by an additional 12 weeks of treatment with Pegasys/ribavirin.
- **Arm D:** 17 patients treated with telaprevir plus Pegasys/ribavirin for 12 weeks – no further treatment.

Medication doses:

- Telaprevir (750 mg (pill) taken



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every 8 hours (or placebo pill)), Pegasys (180 ug injected once weekly), and ribavirin (dosed by body weight at either 1000 or 1200 mg a day).

Patients were followed for a total of 48 weeks. Undetectable HCV RNA was defined as < 10 IU/mL (Roche TaqMan HCV RNA assay). This is an intent-to-treat analysis (all patients who received at least one dose of the study drug).

Results

The sustained virological response (SVR) results for **arms C and D** were released at AASLD. The SVR results from arm A and B will not be available until 2008. But since all the patients have completed therapy, the side effect profile information on the entire patient population in this trial was released.

The SVR (24 weeks post treatment) was **61% in arm C** compared to **35% in the arm D** group.

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In arm C, 8 patients (10%) were lost to follow-up compared to 1 patient (6%) in arm D. Seventy nine percent of those people who had a rapid virological response (RVR – HCV undetectable 4 weeks after starting treatment) in the telaprevir treated groups went on to achieve an SVR.

The most frequent side effects (of all study participants) were rash and pruritus (itching), which were more common and severe in the telaprevir groups. Another frequent side effect was gastrointestinal related and was more common in the telaprevir groups. Thirteen percent of the telaprevir arms discontinued treatment due to side effects during the first 12 weeks compared to 3% in the control arm (arm A). Overall, the incidence of severe side effects was 27% in the telaprevir arm(s) compared to 24% the control arm (arm A).

PROVE 2:

In this study 323 HCV genotype 1 treatment-naïve non-cirrhotic patients in Europe were enrolled. The patients' characteristics were well matched across the treatment arms.

The study participants were randomized into 4 different groups:

- **Arm A:** 82 patients received Pegasys plus ribavirin for 48 weeks (control arm)
- **Arm B:** 81 patients received telaprevir plus Pegasys/ribavirin for 12 weeks followed by another 12 weeks of Pegasys/ribavirin (24 week arm)
- **Arm C:** 82 patients received telaprevir plus Pegasys/ribavirin for 12 weeks (12 week arm)
- **Arm D:** 78 patients received telaprevir plus Pegasys for 12

weeks (no ribavirin arm)

Medication doses:

- Telaprevir (750 mg (pill) taken every 8 hours (or placebo pill)), Pegasys (180 ug injected once weekly), and ribavirin (dosed by body weight at either 1000 or 1200 mg a day). In this study the first dose of telaprevir was 1250 mg followed by the regular dosing above.

The patients were followed for 48 weeks. Undetectable HCV RNA was defined as < 10 IU/mL (Roche TaqMan HCV RNA assay). The analysis is intent to treat. The 36 week interim analysis of this trial was presented at AASLD. The results presented were response rates 12 weeks post treatment. The usual definition of SVR is when HCV RNA is undetectable 24 weeks post treatment. However, the definitions are changing with the newer therapies since it seems that the results seen at 12 weeks post treatment seem to be equal to the results seen week 24 post treatment. However, more data is needed to confirm this 'newer' definition.

Results

The SVR rates were **59% in arm C**, and **29% in arm D**. The SVR 12 week rates were **65% in arm B**. There was also a low relapse rate in those who achieved RVR in the telaprevir groups.

The most common side effects were similar to the side effects reported in PROVE 1 – rash, pruritus (itching), gastrointestinal side effects and anemia. Discontinuation rates were 5% in the Control Arm compared to 10-15% in the telaprevir arms.

Probably the side effect that has received the most attention in both the PROVE 1 and 2 studies is the rash. In the presentation the rash

was described as a maculopapular, which is a rash that is generally flat in appearance, reddish with papules (small raised bumps) and covers a large area of skin. The good news is that the rash resolved after treatment was stopped.

BOTTOM LINE:

These results are very encouraging. The most important information that we have learned from these two studies (besides safety and tolerability) include:

- **Duration of treatment** with the triple combination therapy should be for 24 weeks. Unfortunately, the 12 week treatment group had a higher relapse rate.
- **Ribavirin** is a key to achieving an SVR in this and in every other study seen to date. It also confirms that ribavirin will be a part of the HCV drug cocktail until such time as there are multiple protease and polymerase medications available to replace it.

So what does all this mean? If these results can be confirmed in larger phase III studies (to begin in early 2008) the response rates will be increased by approximately ten percent from the current ~ 50% SVR rates to approximately 60%. At the same time treatment duration could be reduced from the current 48 weeks for genotype 1 to 24 weeks. This is really good news and the approval of triple therapy of telaprevir, pegylated interferon and ribavirin will be a major advancement in the treatment of hepatitis C. If there are no glitches or major problems in the phase III studies there is a very real possibility that the triple combination could be FDA approved by 2010-2011.

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HIV/HCV Coinfection Updates from the 2007 AASLD Liver Meeting



Liz Highleyman

The recent 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), held in Boston in early November, featured several presentations on hepatitis C virus (HCV) coinfection in HIV positive individuals.

LIVER DISEASE PROGRESSION

As HIV positive people live longer due to effective antiretroviral therapy, chronic liver disease has become an increasingly important cause of illness and death. For example, an analysis of mortality among 35,000 HIV positive patients in the French GERMIVIC/MORTIVIC study between 1995 and 2005 (*abstract 135*) found that end-stage liver disease (ESLD) is a major, and increasing, cause of death in this population. In 2005, 18% of all deaths – and 29% of non-AIDS-related deaths – were due to ESLD; 80% of patients dying of liver disease had chronic hepatitis C coinfection.

However, data are still in conflict about whether HIV/HCV coinfecting people experience more rapid liver disease progression than those with HCV alone. While several past studies have indicated that this is the case, others suggest that coinfecting people with well-preserved immune function, indicated by high CD4 cell counts, may fare as well as HIV negative people with hepatitis C.

H. Thein and colleagues (*abstract 1353*) performed a systematic review and meta-analysis of 16 published studies to estimate liver fibrosis progression in HIV/HCV coinfecting people. They determined that the combined probability of developing cirrhosis was 25% after 20 years and 77% after 40 years – higher than the progression rate observed in HCV monoinfected individuals (estimated at about 50% after 50 years).

Accelerated fibrosis progression is particularly pronounced among HIV/HCV coinfecting individuals with low CD4 cell counts. T. Reiberger and colleagues (*abstract 1472*) reported that, overall, coinfecting people had an accelerated fibrosis progression rate and higher portal vein pressure than HIV negative individuals with hepatitis C. But among the HIV positive patients, those with “nadir” (lowest-ever) CD4 counts below 200 – the criteria for an AIDS diagnosis – had faster fibrosis progression than those who had never experienced such severe immune suppression.

Finally, E. Seremba and colleagues (*abstract 1480*) reported that individuals triply infected with HIV, HCV, and hepatitis B virus (HBV) were more likely to develop cirrhosis and experience ESLD compared to those with either HIV/HCV or HIV/HBV dual coinfection.

LIVER CANCER

A. Diaz-Sanchez and colleagues (*abstract 363*) reported that HIV positive patients with hepatocellular carcinoma (HCC) – one potential long-term consequence of chronic HCV infection – have worse prognosis than HIV negative individuals. The researchers conducted a retrospective analysis of 124 patients with HCC seen at a single center in Spain between October 1998 and January 2007 (25 with and 99 without HIV). On the whole, the HIV positive individuals were younger (46 vs 70 years), were more likely to have HCC related to HCV infection (84% vs 64%), had more advanced liver cancer (36% vs 20% with BCLC stage C; 36% vs 1% with stage D), and had shorter survival durations (11 vs 37 months). However, HIV disease severity (indicated by HIV viral load, CD4 cell count, and AIDS diagnosis) had no influence on survival.

These results are similar to findings from a recent North American analysis reported by N. Brau and colleagues in the October 2007 *Journal of Hepatology*. In that study, too, HIV positive patients with HCC were younger (52 vs 64 years), more likely to have chronic hepatitis B or C coinfection, developed HCC sooner after HCV infection (26 vs 34 years), and had more advanced liver cancer. In that study, HIV status did not independently

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COINFECTION

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predict survival, but among those not treated for HCC, HIV positive patients with a lower HIV viral load (below 400 copies) had a longer average survival duration than those with higher HIV RNA levels (7 vs 3 months).

EFFECT OF ANTI-HCV TREATMENT

F. Bani-Sadr and colleagues (*abstract 259*) reported on a prospective study of the long-term benefits of combination interferon-based hepatitis C treatment among 383 HIV/HCV coinfecting patients followed for five years. In general, the participants had well-controlled HIV disease (mean CD4 cell count of 532, two-thirds with HIV viral load below 400 copies). About half had HCV genotype 1 or 4, and the overall sustained virological response (SVR) rate was 29%. After a median follow-up period of 60 months, about 5% developed ESLD (defined as HCC, liver

decompensation, liver transplantation, or death). The risk of ESLD was greater among patients with lower CD4 cell counts (below 350) and slightly reduced among those who achieved SVR, although the latter difference did not reach statistical significance.

Similar results were reported by Y. Benhamou at AASLD (*abstract 1372*) and by S. Dominguez at the recent 11th European AIDS Conference, held in Madrid in late October (*abstract P8/2*). The

researchers retrospectively analyzed 437 HIV/HCV coinfecting patients seen at a large Paris hospital between 1980 and 2006. Slightly more than half received hepatitis C treatment, mostly with pegylated interferon plus ribavirin. After an average follow-up period of 10 years, 38% of treated patients achieved SVR. Patients treated for hepatitis C had a greater likelihood of liver decompensation (14% vs 4%), but this was because those with more advanced liver disease were more likely to receive anti-HCV therapy. Treated patients who achieved SVR, however, had only a 2% risk of liver decompensation. While about 5% of patients died overall, this fell to just over 1% among those who achieved SVR. Among patients with repeated liver biopsies taken an average of about four years apart, the fibrosis progression rate (change in Metavir fibrosis score)

“Together, these studies suggest that HIV plays a direct role in promoting HCV replication and liver fibrosis in coinfecting individuals.”

was lower in treated versus untreated individuals. The progression rate was negative – indicating regression of fibrosis – in patients who achieved SVR. Overall, while the benefits were greatest for individuals with SVR, treated patients benefited compared with untreated individuals even if they did not experience sustained response.

BIOLOGICAL BASIS OF LIVER DISEASE PROGRESSION

Three studies presented at AASLD shed further light on the mechanisms that contribute to more rapid liver fibrosis progression among HIV/HCV coinfecting

individuals.

In a laboratory study, A.C. Tuyama and colleagues (*abstract LB3*) examined whether strains of HIV that use two different coreceptors to enter host cells (CCR5 and CXCR4) are able to enter hepatic stellate cells, liver cells that produce the extracellular matrix proteins responsible for fibrosis. They found that HIV did infect and replicate within hepatic stellate cells, promoting cell activation and increased production of collagen and a protein associated with fibrosis known as alpha-SMA. Stellate cell activation and increased collagen production also occurred when the cells were exposed to HIV envelope proteins, even if HIV did not actually enter the cells.

Likewise, R. Bruno and colleagues (*abstract 125*) demonstrated that exposure to the gp120 envelope protein from CCR5-tropic HIV strains led to hepatic stellate cell activation and increased production of collagen and proinflammatory cytokines. Finally, W. Lin and colleagues (*abstract 469*) reported that exposure to the gp120 protein promoted HCV replication, possibly via upregulation of transforming growth factor-beta (a cytokine that promotes cell proliferation) in HCV-infected hepatocytes.

Together, these studies suggest that HIV plays a direct role in promoting HCV replication and liver fibrosis in coinfecting individuals, and also help explain why liver disease progression may not be accelerated in coinfecting patients with sustained well-controlled HIV replication.



HealthWise:

Supporting your Immune System

(Final in a four part series)



Lucinda K. Porter, RN

This series started with basic viral information and moved on to the immune system. Last month's *Healthwise* featured prevention through hygiene, habits and immunizations. This final installment covers ways to support the immune system.

Many think that the best ways to boost the immune system is with diet and supplements. We know that poor nutrition may weaken immunity, particularly for the frail elderly. However, there is no solid research that proves that any specific food or dietary supplement will stimulate the immune system.

This is not an invitation to start hanging out at the local fast food restaurant. There are plenty of reasons to be careful of what we eat. If you want to enhance your immune system, the two major ways to do this are exercise and stress reduction.

Good health and a well-functioning immune system go hand-in-hand. The formula is simple – the better you take care of yourself, the more likely you will stay healthy. Here are some suggestions for people living with hepatitis C viral infection (HCV):

- Incorporate at least 20 to 45 minutes of moderate physical activity into your daily routine.
- Avoid or reduce stress.
- Avoid alcohol, tobacco and recreational drugs. If you cannot quit, then cut back or get help.
- Aim for 7 to 9 hours of sleep every night.
- Wash your hands – properly and often.
- Keep current with regular medical screenings.
- Be immunized against hepatitis A and B. Make sure all vaccinations are up to date. Get an annual flu shot.
- Maintain a healthy weight.
- Eat a low fat, high fiber diet. Include fruit, vegetables, and whole grains. Avoid trans-fatty acids and saturated fats.
- Cultivate a positive attitude.

- Pursue pastimes that give you pleasure and make you laugh.
- Choose activities that stimulate your brain.
- Engage your spirit in meaningful ways, such as meditation, a walk in the woods, prayer.
- Learn to laugh at yourself.
- Drink 6 to 8 glasses of water every day.
- Practice safer sex.
- Join an HCV support group.
- Maintain friendships and social contacts.
- Help others. Volunteer your time.
- Be grateful and appreciative for what you have in your life.

This is the short list. I might add floss your teeth, use sunscreen, wear seatbelts, know how to swim before diving into deep water, etc. You get the point. Taking care of ourselves can be overwhelming. Factor in poor health, poverty, no access to health care, taking care of kids and aging parents and it is a wonder any of us make it past 40, but we do.

We do because humans are resilient. If you are living with HCV, you are a testimony to this resilience. We live with a virus that replicates a trillion copies every day and yet few of us will die from it.

I wish it were easy to follow all these recommendations, but perfection eludes most of us. For me, developing good health habits is a gradual and ongoing process. It is a journey – not a destination.

As winter approaches, it can be hard to stay motivated. Pick a small goal and try to stick to it for a week. If you meet your goal, try it for another week. Don't start on a new goal until you have practiced this for at least 2 to 4 weeks. Find someone who shares some of your goals. A "health buddy" can help you stay on track.

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IMMUNE SYSTEM

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Vitamin and mineral deficiencies may weaken your health. Ricketts and scurvy are caused by inadequate amounts of vitamins. Insufficient vitamin D is linked to an increased cancer risk. Vitamin D studies look promising; the current research suggests we should raise the Recommended Daily Allowances (RDA) for vitamin D.

If you want more information about dietary supplements, check out the Sloan Kettering Cancer Center website (*see below*). Regular *Healthwise* readers may be tired of my caveats on this subject, but here they are:

- Before you take a supplement, discuss this with your medical provider.
- Do your homework. Research a supplement like you would any medication.
- Before you take a supplement, check to see if it interacts with any other supplements or medications you take.
- Know your source. Herbs may be contaminated. Before ingesting anything, ask yourself what you know about what you are about to take.
- Choose products that are standardized and submitted to voluntary self-regulation.
- Remember that everything goes through the liver. Dietary supplements should *never* be used with decompensated cirrhosis.

Some drugs weaken the immune system by suppressing white blood cell activity and production. Steroids are the most common of these. Unsupervised steroid use is risky. People with transplanted organs need immunosuppressants

to prevent organ rejection. Immunosuppressants are serious drugs reserved for serious situations.

A word about antibiotics – when they are prescribed, make sure you take them all as directed. If you have a 10-day course of pills, do not stop taking them even if you feel better. If you do, bacteria get stronger and more resistant to future treatment. Antibiotics will not help colds or flu. These are caused by viruses – not bacteria. Antibiotics won't kill a virus anymore than a gun will stop a house fire. To stop a virus, you need the right weapon.

There are anti-viral medications, but these are for specific circumstances. Interferon is an anti-viral used to treat HCV infection as well as other viruses. Acyclovir is used for herpes. Anti-virals don't kill viruses directly. Instead, they help the immune system to do this.

Don't wait until the New Year to embrace new health habits – start now. If time is a problem, ask yourself if you have time to get sick. What will happen to your time if you die early because you didn't have time to exercise? Today is the perfect day to begin.

Resources

Note: HCSP and the authors do not endorse the products or advertising on any of these websites.

For more information, look at HCSP's guides and fact sheets at www.hcvadvocate.org

- **Aetna Intellihealth**
www.intelihealth.com This is an excellent resource.
- **Centers for Disease Control**
www.cdc.gov Health and disease information; vaccine recommendations; information about HCV.
- **Family Doctor**
www.familydoctor.org Look at the Healthy Living section.

- **Food Safety**
www.foodsafety.gov 1-888-SAFE-FOOD (1-888-723-3366).
- **Harvard School of Public Health**
www.hsph.harvard.edu/nutrition-source/index.html Offers an alternative food pyramid, nutrition, and healthy lifestyle information.
- **Mayo Clinic**
www.mayoclinic.com Check out the Healthy Lifestyle section.
- **Merck**
www.mercksource.com Although owned by a pharmaceutical company, there is good information and no advertising. Free sign-up is required in order to access some of the information.
- **The National Sleep Foundation**
www.sleepfoundation.org.
- **ShapeUp**
www.shapeup.org This nonprofit organization offers practical information.
- **Partnership for Healthy Weight Management**
www.consumer.gov/weightloss This coalition promotes healthy weight management.
- **PrimusWeb.com**
www.primusweb.com/fitnesspartner Great fitness website.
- **Sloan Kettering Cancer Center**
www.mskcc.org/mskcc Excellent information about supplements.
- **United States Department of Agriculture**
www.mypyramid.gov This website offers interactive tools for personalizing nutritional goals.
- **United States Department of Health and Human Services**
www.smallstep.gov Government-sponsored fitness motivation website.



Disability & Benefits:

Open Enrollment for Employer Plans and Medicare



Jacques Chambers, CLU

This is the time of year when many employers provide an Open Enrollment Period for their employees. Also, from November 15 through December 31 Medicare beneficiaries are able to make changes in their coverages too.

EMPLOYER PROVIDED BENEFIT PLANS (MEDICARE COVERED BELOW)

Not all companies have their Open Enrollment Period at the end of the year, but many do. Companies offering Open Enrollment publish (or offer online) an Open Enrollment Guide that spells out the options and opportunities to make changes as well as the time period during which changes can be made. It is important to read these guides carefully as they will contain all the rules on what choices can be made and how to make them. It also usually gives each employee a summary of his or her present coverage.

For persons dealing with a serious medical condition like HCV, it can be an opportunity to alter benefits and, in some cases, actually increase benefits. Each employer and its insurer will have rules as to what may and may not be added or changed, so be sure to read the Open Enrollment Guide carefully. Some of the possible changes are listed below.

Life Insurance

Persons dealing with HCV are generally unable to purchase life insurance in the individual market. However, some larger employers offer voluntary, supplemental life insurance and open enrollment may offer an opportunity to increase the amount of life insurance an employee purchases without proof of good health. Often, the amount that can be increased without providing such proof is limited to only the immediate next bracket available.

For example, an employer may offer Supplemental Life Insurance in \$20,000 increments. When you first enrolled in the benefits plan, you purchased 3 increments (\$60,000) in Supplemental Life Insurance. At Open Enrollment, you may be able to purchase an additional \$20,000 bringing the total of your Supplemental Life up to \$80,000 regardless of your medical condition.

It is important to carefully read your Open Enrollment material. While many employers offer this option, others will not. If, however, it is available it is an excellent way for an “uninsurable” person to obtain additional life insurance.

Long Term Disability

Less common, but still occasionally available, is the opportunity to increase the benefit of your LTD plan. Some employers will provide a basic benefit for LTD, such as 50% or 60% of your monthly earnings, and allow employees to purchase an additional 10% or 15% to raise the benefit they would receive in the event of disability.

Some employers may allow you to add this benefit if you did not elect it originally. Again, it is important to read your Open Enrollment material to see if your employer offers this.

Some employers may allow you to add this benefit if you did not elect it originally. Again, it is important to read your Open Enrollment material to see if your employer offers this.

Revising LTD Premium Payment

One further possibility to explore is the payment of LTD premiums and its effect on the income taxability of the disability benefits. Some employers will allow you to pay for the LTD coverage through payroll deduction rather than receiving it as a gift. If this is possible you may want to jump at the chance, the reason being taxes.

If you pay for the LTD coverage with money you earn and pay income taxes on, then the benefits you receive if you become disabled will be income tax free, substantially increasing the spendable dollars you would receive as a disability benefit. Conversely, if the employer “gives” you LTD coverage and pays for it, then any benefits you would

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OPEN ENROLLMENT

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receive upon disability are fully income taxable.

Health Related Benefits

Many employers, especially larger ones, offer a variety of health, dental, and vision plans that employees can choose from. At Open Enrollment, you have the opportunity to change your coverage from one plan to another regardless of your medical condition, and sometimes have the opportunity to make choices within your plan, such as increase or decrease the size of the deductible.

For someone dealing with HCV, this can be an important choice, especially if this is the first Open Enrollment since diagnosis. There is no one type of health plan that is best for everyone, but there are two main kinds of plans that employers often offer.

Preferred Provider Organization – These plans provide some coverage for all physicians, but pay more if you choose a physician that has contracted with the insurance company, a Preferred Provider. This plan will give you the greatest flexibility in medical providers, however, it will often cost you more out of pocket for both the monthly premium as well as the plan co-pays and co-insurance.

Health Maintenance Organizations – These plans usually offer the lowest out-of-pocket expenses, but limit your choice of physician. Coverage is only provided when using one of their contracting doctors and hospitals. Also, a Primary Care Physician (also called a Gate-

keeper) oversees all your medical care and must refer you to a specialist before the specialist's charge would be covered by the plans.

MEDICARE

Medicare beneficiaries have several choices as well, and the choices must be made between November 15 and December 31 with all changes effective January 1, 2008.

Original Fee For Service Medicare – Many people elect to stay with original Fee-For-Service Medicare. It consists of Part A – Hospital Coverage; Part B – Medical Coverage; and Part D – Prescription Drug Coverage. Parts A and B of original Medicare are the same for everyone, however, each beneficiary can elect in which prescription drug plan to enroll.

The only way to determine which Drug Plan is best for you is to compare plans using your own prescriptions, since not all plans cover all medications. There is a program on line at www.medicare.gov that allows you to enter your medications and where you live and it will show you what each plan would cost you out of your pocket based on your medications.

For persons who are not comfortable with computers, Medicare's toll-free number (800-MEDICARE) will do the same calculation. However, I recommend you find a friend or relative who will do it for you, because the results are too long and involved for a telephone operator to spend much time reviewing all options.

Medicare Advantage Plans – These are plans offered by insurance companies and health service providers that are an

alternative to Fee-for-Service Medicare. Many of these plans are Health Maintenance Organizations, but there are also Preferred Provider Organization Plans as well as some other types.

Under these plans, Medicare pays the insurance company to provide all of your medical care. Benefits under your red, white, and blue Medicare card are no longer good while you are covered under a Medicare Advantage Plan.

These plans also provide the prescription drug coverage so you don't have to work through the Part D coverage question.

During this Open Enrollment Period, persons may switch from one Medicare Advantage Plan to another or move back to or away from Fee-For Service Medicare.



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BIG THREE

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The results from another telaprevir study called the PROVE 3 study are eagerly awaited. In this study, prior HCV genotype 1 non-SVR responders to treatment with pegylated interferon plus ribavirin are being treated with a triple combination of telaprevir (or placebo), and Pegasys plus ribavirin. The study has completed enrollment and clinical trial results are expected in 2008. This is a really important study especially for those people who have not achieved an SVR and are waiting for new drugs that we all hope will increase the odds of successful treatment for this very large group of people who currently have limited treatment options.

ALBUFERON

The final phase II study results from two studies with albinferon alfa-2b (Albuferon) were released at AASLD. In the first study presented, 458 HCV genotype 1 treatment-naive patients were randomized into 4 groups:

- **Arm A:** Albuferon 900 mcg injected every two weeks
- **Arm B:** Albuferon 1200 mcg every two weeks
- **Arm C:** Albuferon 1200 mcg every 4 weeks
- **Arm D:** Pegasys 180 mcg once a week (control arm)

All patients received weight based ribavirin daily. The treatment duration was 48 weeks and the primary end-point was sustained virological response defined as undetectable (< 10 IU/mL) 24 weeks post treatment.

Results

In the intent-to-treat analysis the SVR rates reported were:

- **Arm A** – 58.5% SVR. The rate of discontinuations due to adverse events was 9.3%.
- **Arm B** – 55.5% SVR. The rate of treatment discontinuations due to adverse events was 18.2%.
- **Arm C** – 50.9% SVR. The rate of treatment discontinuations due to adverse events was 12.1%.
- **Arm D** – 57.9% SVR. The rate of treatment discontinuations due to adverse events was 6.1%

In the second study, 115 prior interferon treatment non-responders were treated with various doses of albuferon plus ribavirin for 48 or 72 weeks of treatment. Unfortunately, the SVR rates were not encouraging for any of the treatment arms (1200 mcg once every 4 weeks, 900 mcg once every 2 weeks, 1200 mcg once every 2 weeks, 1500 mcg once every 2 weeks and 1800 once every 2 weeks) plus weight based ribavirin – overall SVR was 17.4%. This is not surprising since this group of people typically have very low treatment response rates.

Bottom line:

The larger phase III studies will give a better picture of the effectiveness and side effect profile of Albuferon. However, it seems that Albuferon's effectiveness is comparable to pegylated interferon, at least in this study. A couple of big questions remain to be answered – is the convenience of dosing every two weeks

vs. once a week dosing enough of an improvement over current therapy? And is the side effect profile of Albuferon better than pegylated interferon? In a company press release a sub-analysis of the data was done that found that there may be a lower side effect profile with Albuferon and that heavier patients may respond better to Albuferon than to pegylated interferon. But there are a couple of problems with coming to these conclusions. The first problem is that reporting side effects is subjective – one person's idea or experience of a lower quality of life or side effects differs from what another person's experience especially if you consider the small population of 115 patients. The second problem is that it is difficult to come to a conclusion that Albuferon works better in heavier patients because again the number of study participants was relatively small. To help answer the question of the effectiveness of Albuferon in heavier patients, Novartis (Human Genome Science's drug development partner) announced that they are planning a phase 2b study that will hopefully shed more light on this issue. Novartis expects to begin enrollment by the end of 2007.

According to Human Genome Science (HGS) the enrollment in their phase III studies has been completed and results are expected by spring 2009. In the same press release HGS stated that they expect to file for FDA marketing approval in 2010. If there are no glitches in the clinical trials or application process Albuferon could be available to patients by 2011.

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Holiday Wish List and Wyoming Organ Donor Registry

The holidays are upon us and, to some, this means making a gift list. Do you ever wish you could give or receive something more meaningful than a sweater or box of chocolates? Consider giving a priceless gift by signing up to be a potential organ and tissue donor. If someone asks you what you want, ask him or her to register as a donor. If you are lucky, you may also get a box of chocolates. (Dark chocolate is rich in antioxidants, but keep it to one piece a day.)

It is easy to register as a potential organ and tissue donor if you live in the State of Wyoming. Visit www.wyomingdonorregistry.org for more information. At that web site, there is a quote by 14-year-old Ruth Ellen. "Give another season of life. Be an organ and tissue donor." This is a holiday message worth hearing.

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R1626

Another new HCV medication that has generated a lot of excitement is R1626. R1626 is an HCV polymerase inhibitor. The results from the POLI.1 study were released at AASLD. In this study 100 HCV genotype 1 treatment-naïve (non-cirrhotic) patients were randomized into 4 different treatment arms:

- **Arm A:** 20 patients received 1500 mg R1626 bid (twice daily) plus Pegasys,
- **Arm B:** 30 patients received 3000 mg R1626 bid plus Pegasys,
- **Arm C:** 30 patients received 1500 mg R1626 bid in combination with Pegasys/ribavirin (triple combination),
- **Arm D:** 20 patients were treated with Pegasys/ribavirin (control arm)

Ribavirin was weight based (1000/1200 mg/day) and Pegasys by injection once a week.

In arms A, B, and C study participants received R1626 for 4 weeks followed by Pegasys/ribavirin for an additional 42 weeks. The participants in the control arm were treated for 48 weeks. HCV RNA undetectable was defined as < 15 IU/mL with Roche COBAS TaqMan HCV Test.

After 4 weeks of treatment the percentage of people who were undetectable was **33% (arm A)**, **69% (arm B)**, and **81% (arm C)** compared to **5% in the control group (arm D)**. Fifty percent of the patients in the R1626 arms achieved normalization of ALT levels.

There were 8 patients who had viral rebound (viral load went from undetectable to detectable), but these were only in people who had stopped taking R1626. In all of the people who took R1626 none developed drug resistant mutations.

The side effects were considered mild to moderate with the most serious adverse event being Grade 4 neutropenia (low white blood cells), which was the major reason for dose reductions and treatment discontinuations. The degree of neutropenia was not associated with infection and the neutrophil counts rebounded significantly after stopping R1626.

Bottom line:

R1626 does not appear to produce drug resistance and when used in combination with Pegasys and ribavirin the viral load reductions are very impressive. The combination of these factors makes it a very good candidate for advancement into larger clinical trials. However, the side effect profile is a cause for concern, especially the incidence of neutropenia. In response to these concerns, Roche announced that it is conducting another phase 2b study of R1626 in 490 patients to test different doses of R1626 (500,1000 and 1500 mg bid), and Pegasys (90 ug and 180 ug) plus standard ribavirin dosing to find the best dose(s) that will produce the highest response rates, but that will also minimize the side effect profile.

In next month's *HCV Advocate* I will continue this report on the data on new drugs that was presented at AASLD 2007.



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