Sustained response to treatment reduces fatigue in hepatitis C patients

By Liz Highleyman

Curative treatment that eliminates hepatitis C virus (HCV) from the body can reduce central fatigue, one of the most concerning symptoms associated with chronic hepatitis C, according to research presented at the 49th annual meeting of the European Association for the Study of the Liver (EASL), held recently in London.

Fatigue is a common and debilitating symptom for many people with hepatitis C. Central fatigue refers to weakness originating in the central nervous system (the brain and spinal cord), as opposed to peripheral or physical fatigue that originates in the muscles.

Fatigue is also a common side-effect of treatment with interferon and ribavirin. Ribavirin often causes anemia, which can lead to fatigue by reducing the blood’s capacity to carry oxygen. New direct-acting antiviral agents allow people with hepatitis C to either take interferon or ribavirin for a shorter duration or to avoid them altogether.

Zobair Younossi and colleagues with Inova Health System in Virginia evaluated changes in fatigue among people with hepatitis C treated and cured with sofosbuvir, either with pegylated interferon and ribavirin in the NEUTRINO trial (genotypes 1, 4, 5 and 6) or with ribavirin alone in the FUSION trial (genotypes 2 and 3).

The analysis included 413 people who achieved sustained virological response, or undetectable HCV RNA at 12 weeks after finishing treatment (SVR12). About 60% were men, most were white, the mean age was 52 years and 18% had liver cirrhosis. At baseline, 12% of study participants reported fatigue, 18% reported anxiety and 24% each reported insomnia and depression. During treatment 87% developed anemia (a hemoglobin decrease of 2 g/dL or more).

Fatigue was assessed using three validated questionnaires: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV) and Short Form-36 (SF36). The researchers focused on items related to both central fatigue (four items) and peripheral fatigue (nine items).

After achieving sustained response, participants reported significant improvement in fatigue compared to their pre-treatment scores using all questionnaires: average 26.9% improvement on the SF36 vitality scale, 19.8% on the FACIT-F fatigue scale and 10.7% on CLDQ-HCV activity-energy domain. All items in the questionnaires related to central fatigue showed improvement, while only two items related to peripheral fatigue did so.

In addition, after successful treatment the proportion of patients who scored below the general population norm decreased using all questionnaires: from 32.7% to 27.6% on the SF36 vitality scale, from 19.8% on the FACIT-F fatigue scale and 10.7% on CLDQ-HCV activity-energy domain.

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Even moderate drinking increases risk of advanced liver fibrosis for people with HIV and HCV co-infection

By Michael Carter

Even moderate alcohol consumption is associated with an increased risk of advanced liver fibrosis for people living with HIV and hepatitis C virus (HCV) co-infection, investigators from the United States report in Clinical Infectious Diseases. For all categories of drinking – moderate, severe/binge and alcohol-related disorders – prevalence of advanced liver fibrosis was also higher among people living with HIV or HCV mono-infection compared to people who had neither infection.

“For each alcohol use category, advanced fibrosis was more common among HIV-infected than -uninfected and chronic HCV-infected than -uninfected patients,” comment the authors. “When we evaluated associations between alcohol use categories and advanced fibrosis across groups stratified by HIV/HCV status, the strongest associations were observed among those with HIV/HCV coinfection.”

The investigators believe their findings have important implications for patient care, and that individuals with advanced fibrosis should be advised to abstain from alcohol use or reduce their drinking.

Alcohol consumption is highly prevalent among people living with HIV and/or HCV infection, and heavy drinking has been associated with advanced liver disease in this group. However, the impact of different levels of alcohol consumption on the severity of liver fibrosis in people living with HIV and/or HCV infection is unclear. Investigators from the US Department of Veterans Affairs therefore designed a cross-sectional study to evaluate the associations between different levels of alcohol consumption and advanced liver fibrosis in patients according to their HIV and/or HCV infection status.

Participants were recruited to the study between 2002 and 2010. The study population included 701 people with HIV and HCV-co-infection; 1410 people with HIV mono-infection; 296 people with HCV mono-infection and 1158 people with neither infection (controls). All reported some level of alcohol consumption. Liver fibrosis was assessed non-invasively using the FIB-4 index, a score above 3.5 indicating advanced fibrosis. Participants completed a short questionnaire about their alcohol consumption and were placed into one of three categories: non-hazardous drinking; hazardous/binge drinking; alcohol-related disorders.

Overall, 8% of participants had advanced liver fibrosis. Prevalence was higher among people with HIV (10%) than people who did not have HIV (4%) and also among people with chronic HCV infection (19%) compared to people who did not have HCV (4%).

For all patient groups, the prevalence of severe fibrosis increased with alcohol use category.

Moreover, for each alcohol use category, advanced fibrosis was more common in HIV-positive than HIV-negative patients (non-hazardous: 7 vs 1%; hazardous/binge: 10 vs 3%; alcohol-related disorders: 19 vs 9%; p < 0.01). Findings were similar when the investigators compared HCV-infected and -uninfected patients (non-hazardous 14 vs 3%; hazardous/binge: 18 vs 3%; alcohol-related disorders: 22 vs 7%; p < 0.01).

Continued on page 14
Second analysis concludes HIV transmission from someone on long-term treatment

By Gus Cairns

A study that estimates the risk that someone living with HIV and taking antiretroviral therapy could transmit the virus reports that, on the basis of the few transmissions from heterosexual partners on treatment that have been reported, it is not possible to dismiss the risk of infection as zero.

The analysis by French researchers in Clinical Infectious Diseases estimates that the highest-likely risk of HIV being transmitted is between 8.7 and 13 transmissions per 100,000 sex acts; in other words, from one in about 11,500 to one in about 7700 acts. However, the researchers stressed to aidsmap.com that this is the highest-likely risk: the actual risk may be lower than this and could indeed be zero.

This implies that the accumulated highest-likely risk of HIV transmission would rise to 1% after between 195 and 389 occasions of sex: a couple who have vaginal sex around six times a month would take two and a half years to have sex 195 times, or five and a half years to have sex 389 times.

This is the second recent study to find that the long-term risk from a partner on antiretroviral therapy (ART), while very much lower than from a partner not on treatment, may not be negligible in the long term.

The other study, by the Centers for Disease Control and Prevention (CDC), used a mathematical model to calculate the one- and ten-year risks of HIV infection in heterosexual and gay couples. It then added in the mitigating effects of ART, condom use, circumcision and pre-exposure prophylaxis (PrEP). It used estimates of the likelihood of transmission, and the efficacy of the different prevention methods, from various studies.

The French researchers tackled the question by searching out the few actual reported cases of HIV transmission within a heterosexual couple where the partner living with HIV was on ART, and where the virus was unequivocally shown to have come from them. They then calculated the highest-likely probability of transmission from someone on ART based on these cases.

The researchers found six studies that were set up sufficiently well to document such cases. They identified four cases of viral transmission from a partner on ART during 2773 person-years in 1672 heterosexual, serodiscordant couples. (An additional 182 transmissions occurred when people were not taking ART.)

Four of the studies took place in Africa and one each in Spain and Brazil. Between 70 and 100% of study participants had an undetectable viral load at various time points. At the start of the studies, sexual frequency in participants varied from three to twelve times a month; the American model assumed an unvarying frequency of six times a month.

In three of these transmissions, which were proven to come from the HIV-positive partner by genetic analysis, that partner had been taking ART for less than six months. In the fourth transmission, the person had been taking ART for less than a year. As the Swiss statement says that people who have had an undetectable viral load and no sexually transmitted infections for more than six months may be regarded as non-infectious, the researchers did two calculations for the likelihood of transmission risk, based on whether the transmission in that study had taken place less or more than six months after the start of therapy. This explains the two figures cited for the highest-likely risk of transmission of 8.7 or 13 transmissions per 100,000.

The researchers’ calculation that the chance of transmission from a partner on treatment in a heterosexual couple could rise up to 1% after 195 to 389 occasions of sex allows a comparison with the American model.

The CDC estimated the ten-year risk of HIV transmission from a partner on ART to be 2%. According to the French researchers, the highest-likely risk after 720 sex acts (equivalent to ten years in the US model) was either 1.85% or 3.7% (depending on the timing of that one transmission). This is compatible with the American estimates, though the CDC study computes an average risk of transmission from rather conservative assumptions about the efficacy of different prevention methods, while the French study computes a range of risk, from zero (the lowest-likely risk)
People with HIV are living longer than ever before with improved antiretroviral (ARV) therapies. As patients age, however, other health conditions become more common, such as heart disease, high cholesterol, high blood pressure, diabetes, osteoporosis, kidney disease, and non-AIDS related cancers. These medical conditions may result from aging in general, long-term side effects of ARVs, risk factors that are more common in HIV-positive patients, or the virus itself.

With older age, the number of medications patients require tends to increase. They may also be taking vitamins, supplements, and complementary and alternative medicines (CAM) in addition to their prescription medications. As the number of medications grows, the potential for drug-drug interactions increases.

First things first
To better understand drug interactions, it’s helpful to know something about the chemical reactions that may cause them. Several ARVs may be more likely to cause drug interactions because of their effects on CYP (pronounced “sip”) enzymes.

Cytochrome P450 (CYP450) enzymes are a family of enzymes which work to break down medications in the liver.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are moderate inducers of CYP3A4 enzymes, which means they can speed up how quickly the liver breaks down drugs such as protease inhibitors (PIs) or other drugs that are broken down by this pathway. The concern is that if ARV drug levels become too low, this may lead to viral breakthrough (detectable viral load), development of ARV resistance, or less than ideal disease management.

Conversely, PIs are strong CYP450 inhibitors and can slow down the metabolism of other drugs resulting in increased drug concentrations. This in turn may lead to a greater chance of side effects.

Multiple drugs and aging
Here in Toronto, we conducted a recent study, along with our colleagues, comparing the frequency of potential ARV interactions in HIV-positive people who were 50 years of age or older versus HIV-positive adults who were younger than 50. Fifty years of age was used as the definition of “older,” as patients with HIV may age prematurely.

The study included 914 HIV-positive patients attending the specialist-based immunodeficiency clinic in Toronto General Hospital. Fifty-four percent were younger than 50.

When current medications were compared between older and younger patients, older patients were taking more medications than younger ones, nine compared to seven drugs, and this was a statistically significant difference. Older patients were also more likely to be on a ritonavir (Norvir)-boosted PI or an integrase inhibitor.

They were also taking a greater number of non-ARV medications. These non-HIV therapies included antibiotics, blood thinning agents, drugs for heart disease, antidepressants, mood stabilizers, sedatives, stomach medications, bone medications, narcotics and other painkillers, hormonal drugs, and CAM.

In this study, factors associated with the chance of having one or more potential drug-drug interaction (PDDI) included older age, greater number of non-ARV medications, use of drugs for heart disease, and use of a boosted or unboosted PI.

Moreover, for every 10-year increase in age the odds of identifying one or more PDDI was nearly two times higher (1.72) after taking into account gender, race, and type or number of ARVs.

In contrast, the use of an integrase inhibitor was associated with a decreased probability of one or more PDDI.

ARV effects
A common finding in published studies is that the use of PIs is associated with a higher risk of having an interaction. Ritonavir specifically may be involved in potential drug-drug interactions with a variety of drug classes because it is a potent inhibitor of CYP3A4 and p-glycoprotein (a substance that helps pump drugs and toxins out of cells). Ritonavir also induces numerous enzymes including CYP1A2, CYP2B6,
Continued from page 4

CYP2C9, CYP2C19, and glucuronyltransferase. The results of this study indicate almost half of the patients (44 percent) had PDDIs involving ritonavir, and patients on ritonavir-boosted PIs were 40 times more likely to have a PDDI than patients not taking these drugs.

On the other hand, integrase inhibitors, specifically raltegravir (Isentress), were associated with a decreased likelihood of a PDDI. This is not surprising given raltegravir’s lack of inducing or inhibiting effects on the CYP450 enzyme system.

The newest integrase inhibitor, dolutegravir (Tivicay), also does not significantly affect the cytochrome P450 enzyme system, and is also associated with a low risk of drug interactions.

In contrast, the integrase inhibitor elvitegravir (available only in Stribild) needs to be given with the booster cobicistat. Cobicistat acts similarly to ritonavir in inhibiting CYP3A4 and p-glycoprotein, and may therefore be associated with a higher risk of possible interactions.

Interactions
We found no statistically significant difference in “red flag” drug interactions by age. “Red flags” were defined as medication combinations that are contraindicated, or not to be taken together.

Older patients, however, were more likely to have one or more “orange flag” interactions. “Orange flags” included combinations that should not be taken together, could be given with dose adjustment or increased monitoring, or have not been studied for safety, efficacy, or clinical significance. Orange flag PDDIs were found for 71% of older people compared to 55% of younger individuals.

Patients with orange flag PDDIs were on more ARVs (four compared to three) and were more likely to be virally suppressed compared with patients without PDDIs (92 percent versus 87 percent), possibly due to the greater number of ARVs taken by this group.

Since older patients have been shown to be more adherent to ARVs, this may be another reason for increased virological suppression in patients with orange flag PDDIs in this study as compared to other published research.

Specific interactions
In total, 1,718 potential drug-drug interactions (PDDIs) were identified in 63 percent of patients. Of those, 24% occurred between ARVs and the majority, 76%, were between ARVs and non-ARVs.

A total of 31 red flag PDDIs were identified in three percent of patients. Fourteen involved a PI and an NNRTI which could have resulted in reduced PI levels and viral breakthrough. Seven patients had a red flag PDDI between salmeterol and a PI. Three patients were on combination ritonavir and Levitra (vardenafil), whereas two patients were on Lexiva (fosamprenavir) and Valium (diazepam). The remaining patients had a red flag interaction between a PI and Cordarone (amiodarone), for atrial fibrillation, Zocor (simvastatin), and Halcion (triazolam).

Of a total of 571 orange flag PDDIs found in 62 percent of patients, the most common were: between PIs and nucleosides (28%); medications for heart disease (23%); narcotics (17%); and antidepressants (13%). The most common examples were combinations of ritonavir and analgesics or narcotics (17%), Reyataz (atazanavir) and Viread (tenofovir) (13%), and ritonavir with antidepressants (10%).

Older patients were more likely to have PDDIs involving: Sustiva or Atripla (containing efavirenz) or Intervence (etravirine) with Lipitor (atorvastatin); PIs with calcium channel blockers or statins (heart and cholesterol medications); and ritonavir with beta-blockers (high blood pressure drugs).

An overall look
Overall, this study demonstrated that HIV-positive patients at a specialty clinic treated with ARV therapy are at high risk for experiencing a PDDI. Two-thirds of the patients on ARV therapy had one or more PDDIs identified, with a median of two PDDIs per patient (half of the patients had more than this and half had less). Potential consequences of these interactions included higher risk of drug toxicity or reduced drug effectiveness.

The rate of orange flag interactions was found to be slightly higher in this study when compared to other studies. This may be due to the fact that PDDIs with questionable clinical significance were included; around 8% of orange flag PDDIs in this study fell into that category.

In this study, older patients were significantly more likely than younger patients to be male, men who have sex with men, white and non-immigrants, have a
Doctoral student scores high with innovative HIV research

By Michele McDonald

After a decade in the biotech industry, Gavin Sampey turned to George Mason University because he wants to be on the ground floor of innovative research that could change lives.

“I want to use science to help people,” says the Mason doctoral student, who is working on HIV research at the George Mason-based National Center for Biodefense and Infectious Diseases.

Sampey landed a nearly $62,000 grant from the National Institutes of Health to study how HIV can manipulate the cells’ communication system to work itself up to the brain.

The research is at the forefront; the grant’s score from NIH is a stand out. Sampey may be the first Mason student to receive the elite one percent rating—making it the best of the national grants reviewed, says Fatah Kashanchi, director of research at NCBID and Sampey’s mentor.

“I was very honored,” says Sampey, who was born in Washington, D.C., and grew up in Springfield, Va.

Sampey credits Kashanchi’s guidance through the grant writing process, especially critical reviews of the initial drafts, helped him nab the high score.

“We’re proud of Gavin’s achievement,” Kashanchi says. “Earning the highest honor from the peer review at the National Institutes of Health shows the high quality of work that Mason students are doing and how their promising research may lead to better treatments for patients with debilitating diseases.”

Specifically, the top one percent score is for a grant application for a Ruth L. Kirschstein National Research Service Award (NRSA) Individual Pre-doctoral Fellowship with the National Institute of Neurological Disorders and Stroke, which is part of the NIH, for “Effects of Exosomes Derived from HIV-1 Infected Cells on Viral Spread.”

Sampey’s work looks at exosomes, which are fatty packages of proteins and RNA excreted by a cell to communicate with other cells over long distances. For example, a cell in the intestines can send exosomes to lymph nodes with key information about potential infections.

The HIV virus manipulates the cell’s natural communication process to spread the word to infect healthy cells with HIV. “They prime healthy cells for infection,” Sampey says.

Sampey is researching how these virally altered exosomes may affect brain cells. Nearly half of HIV patients show cognitive disorders with some developing Alzheimer’s-like dementia. Even if a drug regimen suppresses the HIV virus from becoming AIDS, dementia still can happen, Sampey says.

The research’s goal is to create new treatments that target these HIV-altered exosomes and reverse the neurological damage in patients. Making new discoveries that can change lives is why Sampey decided to earn his doctorate after working for a decade at local biotech firms. His past experience in the biotech industry focused more on chemical engineering than ground-floor science.

Press release from George Mason University
NHF is coming to DC this fall

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Funds are limited. Deadline: August 1, 2014.
‘National dialogue’ urged on cost of new HCV drug

By Julie Appleby
Kaiser Health News

The outcry continues over the $1,000-a-pill hepatitis C drug made by California-based Gilead Sciences.

While the drug is a significant advance over older treatments for the viral liver disease, the price set by the company “represents an abuse of market power,” said John Rother, president and CEO of the National Coalition on Health Care, which includes businesses, unions, insurers, consumers and some drugmakers, including the Generic Pharmaceutical Association.

The group recently urged a “national dialogue” on the cost, saying Sovaldi’s price tag threatens the budgets of government run-health programs as well as the premiums for everyone who has private insurance.

With more such “specialty drugs” in the pipeline for other conditions that affect millions of people, the group says the drug industry must find “a more sustainable approach” on prices for new products – although it stopped short of giving examples of how that might be done.

The U.S. currently spends more than $300 billion on pharmaceuticals each year. Simply covering the cost of Sovaldi for the more than 3 million Americans who are estimated to have hepatitis C could double that.

Gilead has staunchly defended Sovaldi’s price, saying the cost – at least $84,000 for a typical patient – is justified because the drug is curative for many and could slow health spending on costly complications of hepatitis over time.

“Sovaldi … represents a finite cure, an important point to consider when comparing the price of a pill or bottle to the lifetime costs of treating a chronic disease,” said spokeswoman Cara Miller. Paying for the new drug will fall on private insurers, and taxpayers through government programs such as Medicaid and Medicare, and could also lead to higher premiums.

All insurers are currently setting guidelines for the use of Sovaldi and another new costly hepatitis C drug called Olysio. While some are making it broadly available, others are saying some patients with mild liver damage should wait for treatment. More hepatitis C drugs are expected on the market as early as this fall – and, unlike Sovaldi, may not require the use of additional drugs that add costs as well as difficult side effects.

The drug industry has long noted that prices reflect the cost of researching and developing drugs. The industry is on the offense, with its lobbying arm saying in a blog post Wednesday that prescription drugs account for only 9 cents of every dollar spent on healthcare. The Pharmaceutical Research and Manufacturers Association of America is also circulating charts this week touting advances in cancer treatments – and noting that the average sales price of cancer drugs covered by Medicare has not risen faster than medical inflation.

If all drugmakers were to justify high prices by saying their products could reduce costs over time by preventing complications, “it could bankrupt the system,” said Rother.

Rother says that officials from Gilead have talked with his group, but so far only in a “defensive” posture over the price. Instead, he wants them to “engage” in conversations about ways to lower the drug’s price.

The coalition joins others – notably pharmacy manager Express Scripts – in calling for a “national dialogue” on drug pricing, although it could not point to an example where that has lowered drug prices in the past.

Prices for drugs in the U.S. are generally what the market will bear – and the market is snapping up Sovaldi even at its high price. In first quarter earnings, Gilead said the drug brought in $2.1 billion in revenue.

“This is an issue other countries have solved,” said Debra Whitman, executive vice president of policy at AARP and a board member of the coalition. She noted that Sovaldi costs $66,000 per 12-week treatment in Germany and $57,000 in Great Britain.

Among the differences in those countries is that regulators are far more involved in approving drugs for use in national health plans – and negotiating how much is paid for them. In England, for example, the cost as well as the effectiveness of drugs is part of the evaluation about whether to approve them for use in the national plan.

Continued on page 11
HIV infection increases risk of melanoma

By Michael Carter

HIV infection is associated with an increased risk of melanoma, according to the results of a meta-analysis published in PLOS ONE. Overall, people living with HIV had a 26% increase in their relative risk of melanoma compared to the general population, the risk increasing by 50% for white-skinned people with HIV. The increased risk was statistically significant in white-skinned people diagnosed with HIV and of borderline statistical significance for all people diagnosed with HIV.

The authors recommend that fair-skinned people living with HIV should be regularly screened for suspicious skin lesions and should also be warned about the dangers of prolonged exposure to the sun.

Melanoma (skin cancer) diagnoses have increased markedly in the UK and many other countries in recent years. There is also evidence suggesting that people living with HIV have a higher risk of developing this skin cancer compared to individuals in the general population. Studies conducted before effective antiretroviral therapy became available in the mid-1990s showed that having HIV increased the relative risk of melanoma by approximately a quarter.

However, it is uncertain whether people living with HIV continue to have an increased risk of melanoma in the era of effective antiretroviral treatment.

A team of Australian and UK investigators therefore conducted a systematic review and meta-analysis, looking at the association between HIV and the relative risk of melanoma in the periods before and after potent HIV therapy became available.

The investigators’ analysis included cohort studies involving adult patients.

A total of 21 studies met their inclusion criteria. These were conducted between 1999 and 2013. Most (twelve) were conducted in the United States, eight in Europe and one in Australia. Most of the studies reported on cohorts of patients with HIV and those diagnosed with AIDS, but six studies defined their study population as patients with AIDS. The majority of studies (16) were population based, most of the patients being men (76-92%). One study included only men who have sex with men; one study included women only; a single study was restricted to veterans and two studies reported on single-clinic patient cohorts.

The median duration of follow-up ranged between two and ten years.

Eight studies presented melanoma estimates for the period before effective HIV therapy became available, the others gave estimates for the period after potent antiretroviral treatment was introduced. Overall, the standard of research was high and 57% of the studies were assessed as high quality and the others were of moderate quality. The most common limitation was a failure to control for ethnicity.

Pooled results showed that, in the era of effective antiretroviral treatment, HIV or AIDS was associated with an increase of borderline significance in the relative risk of melanoma (1.26; 95% CI, 0.97-1.64). This was significant in studies that considered ethnicity (1.50; 95% CI, 1.12-2.01). There was significant heterogeneity between the findings of these studies (p = 0.004).

Examination of data from the pre-therapy era showed that HIV or AIDS significantly increased the overall risk (1.26; 95% CI, 1.11-1.43) of melanoma and that the risk was also significantly increased in studies that controlled for ethnicity (1.28; 95% CI, 1.10-1.49).

These findings remained robust in sensitivity analyses.

“Taking into account the potential confounding effects of ethnicity, our findings show that risk of melanoma in those with HIV/AIDS remains elevated in the HAART [highly active antiretroviral therapy] era, with a 50% increased risk,” comment the authors. “The increased risk of melanoma in populations with HIV/AIDS may be related to effects of HIV infection on the immune system although these are complex, including not only immunodeficiency, but also chronic immune activation and inflammation, and immune dysfunction and senescence [ageing].”

They conclude, “white skinned people with HIV/AIDS would benefit from regular screening of the skin for suspicious pigmented lesions, and since they also have a significantly increased risk of developing
Sofosbuvir for hepatitis C works well despite multiple negative predictive factors

By Liz Highleyman
aidsmap

Hepatitis C treatment using sofosbuvir (Sovaldi) is highly effective even for people with multiple factors traditionally associated with poor response. Having four or more negative predictive factors, however, raises the risk of post-treatment relapse, according to a report at the 49th annual meeting of the European Association for the Study of the Liver (EASL) held recently in London.

The advent of direct-acting antiviral agents (DAAs) has begun to revolutionize treatment for chronic hepatitis C. But several aspects of treatment—including the optimal duration of therapy and the best regimens for patients traditionally considered difficult to treat—are not yet fully understood.

Graham Foster of Queen Mary University of London and colleagues looked at the influence of various host and virus factors traditionally associated with poor response to interferon-based therapy.

Interferon, formerly the mainstay of treatment for chronic hepatitis C, works by stimulating the body’s own immune response against the virus. Direct-acting antivirals directly interfere with different steps of the hepatitis C virus (HCV) lifecycle. Studies have shown that some of the factors associated with poor response to interferon may not have as much effect when using DAAs.

Traditional negative predictive factors include:

- **Viral genotype**: HCV genotypes 1 and 4 have been considered harder to treat than genotypes 2 or 3.
- **Viral load**: high pre-treatment HCV RNA (>800,000 IU/ml) is associated with poorer response.
- **Sex**: men do not respond as well as women.
- **Age**: older people do not respond as well as younger people.
- **Race/ethnicity**: people of African descent (and Hispanic/Latino people in some studies) do not respond as well as Caucasian or Asian people.
- **Body weight**: heavier people, especially those classified as obese (body mass index >30), do not respond as well.
- **IL28B status**: people who carry the TT or CT genetic variations do not respond as well as those with the favorable CC pattern.

- **Liver damage**: people with advanced fibrosis (stage F3) and especially cirrhosis (F4) do not respond as those with absent to moderate fibrosis (F0-F2).
- **HIV/HCV co-infection**: people with both HIV and HCV do not respond as well as those with HCV alone.
- **Prior treatment**: People who previously showed modest or minimal response to prior interferon-based therapy (partial and null responders) do not respond as well as previously untreated (treatment-naive) people or those who previously responded but relapsed after finishing treatment.

Sofosbuvir leads to high response rates for most patient populations. However, a small proportion of people do not achieve sustained virological response, or undetectable HCV RNA at 12 weeks post-treatment (SVR12), which is considered a cure. In most cases this is due to relapse, or viral rebound after treatment is finished.

Foster and his team performed a retrospective meta-analysis of data from phase 2 and 3 clinical trials of sofosbuvir, used with either pegylated interferon and ribavirin (ATOMIC, NEUTRINO) or ribavirin alone (FISSION, POSITRON, FUSION, VALENCE).

The researchers first performed a univariate analysis to see the effect of each factor by itself, then did a multivariate analysis to look at how these factors interact. Finally, they calculated cure rates for people with increasing numbers of negative predictive factors.

The analysis included 339 treatment-naive patients with genotype 1 chronic hepatitis C treated with sofosbuvir plus pegylated interferon and ribavirin for 12 weeks, 285 treatment-experienced and treatment-naive patients with genotype 2 treated with sofosbuvir plus ribavirin for 12 weeks, and 247 treatment-naive and treatment-experienced patients with genotype 3 treated with sofosbuvir plus ribavirin for 24 weeks.

Overall, about 60% of participants were men and about two-thirds were age 50 or older. Fifteen percent of people with genotype 1, 8% of people with genotype 2 and no patients with genotype 3 were black. Approximately 60 to 70% had unfavorable IL28B gene variants. About 16% of people with geno-
type 1 and 2 had cirrhosis, rising to 24% for those with genotype 3. One-third with genotype 2 and 58% with genotype 3 were treatment-experienced (previously treated people with genotype 1 were not included). More than three-quarters had high baseline HCV viral load.

In a univariate regression analysis of the combined data set, factors found to be significantly associated with post-treatment relapse (p < 0.05) were: liver cirrhosis (odds ratio [OR] 4.3, or more than 4-fold higher risk), baseline HCV RNA >800,000 IU/ml (OR 3.9), male sex (OR 3.5), weight over 75kg (OR 3.2), IL28B non-CC (OR 2.8), prior treatment (OR 2.8) and age over 50 years (OR 1.9). The effects of black race, Hispanic ethnicity and elevated baseline ALT were not statistically significant.

Surprisingly, while having HCV genotype 3 rather than 2 was a significant risk factor (OR 2.5), the differences between genotype 1 vs 2 and between 3 vs 1 did not reach statistical significance (p = 0.18 and 0.06, respectively). Nor did HCV subtype 1a vs 1b turn out to be significant in a more restricted analysis of people with genotype 1 (p = 0.14).

In a multivariate regression analysis of the combined data set, only six factors were independently associated with relapse: high baseline viral load (OR 4.7), cirrhosis (OR 4.0), IL28B non-CC (OR 3.4), weight over 75kg (OR 2.5), prior treatment (OR 2.3) and male sex (OR 2.3).

SVR12 rates were 100% for people with zero or one negative predictive factor, above 99% for those with two factors and 94% for those with three factors. After this, efficacy dropped off, falling to 88% for those with four negative factors, 68% for those with five factors and 57% for those with six factors.

Cure rates were 90% or higher for all genotype groups with zero to three negative predictive factors. For those with four or more factors, the effect was most pronounced among people with HCV genotypes 1 or 3 (in fact, no genotype 1 patients had zero risk factors).

"Sofosbuvir-based regimens were highly effective, even in patients with a combination of multiple negative factors," the researchers concluded. "SVR12 rates were comparatively lower in patients with five or six of the negative predictors."

"Patients need to have a cluster of poor predictors to be at risk for failure," Graham Foster explained. He suggested that these factors "may help guide us in an interferon-free world" when deciding on what regimens to use and for how long.

Notably, this analysis is specific to sofosbuvir, an HCV polymerase inhibitor. Other trials indicate that the negative predictive factors which remain relevant may differ among the various DAAs.

Although HIV and HCV co-infection was not included in this analysis, other studies have shown that people with HIV can respond to interferon-free regimens as well as people with HCV alone, leading some experts to suggest that people with co-infection should no longer be separated out as a 'special' or difficult-to-treat population.

Reference

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Rother said the coalition is not calling for price controls and doesn’t think Congress should get involved. “They don’t need to have a direct role,” said Rother. But, he cautioned, if negotiations with drugmakers fail, the industry will ultimately find itself facing lawmakers. “The hope is we can resolve this quickly and through the private sector,” he said.

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keratinocyte skin cancers (at least two-fold) they should be counseled to avoid excessive sun exposure.”

Reference

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Low vitamin D concentrations associated with poor clinical and virological outcomes among people starting HIV therapy

By Michael Carter

Low vitamin D concentrations are associated with an increased risk of HIV disease progression among people starting antiretroviral therapy, investigators report in the online edition of The Journal of Infectious Diseases. Virological failure also had an association with low vitamin D levels at the start of therapy, and there was evidence suggesting a relationship with between vitamin D levels and immunological outcomes. The study was conducted in eight low- and middle-income countries and the US. The authors believe that studies exploring the impact of vitamin D supplementation on HIV treatment outcomes are warranted.

Concentrations of vitamin D are related to exposure to sunlight, latitude, season and skin pigmentation. The vitamin is important to a healthy immune system. Several studies involving people living with HIV have shown a high prevalence of low vitamin D concentrations.

However, few studies have examined the relationship between low vitamin D concentrations at the initiation of antiretroviral therapy and clinical outcomes. The connection between baseline vitamin D levels and virological and immunological outcomes is unexplored.

Data collected during the PEARL (Prospective Evaluation of Antiretrovirals in Resource Limited Settings) study provided information for investigators to explore the relationship between low baseline vitamin D levels and treatment outcomes.

The study population consisted of people living with HIV who experienced progression to WHO (World Health Organization) stage 3/4 disease within 96 weeks of starting therapy; people who experienced virological failure (two consecutive viral load measurements above 1000 copies/ml 16 weeks after initiating treatment); and people with immunological failure (CD4 count below 100 cells/mm3 after 48 weeks of treatment). These patients were compared to randomly selected individuals to see if baseline vitamin D levels were associated with an increased risk of poorer outcomes.

Recruitment took place between 2005 and 2007. Participants were enrolled in Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, the United States and Zimbabwe.

Almost half (49%) of all participants in the study had low vitamin D concentrations at baseline. Prevalence of low vitamin D varied between countries, ranging from 27% in Brazil to 78% in Thailand and 72% in India. Prevalence was 92% among African-Americans in the US.

After controlling for country and HIV treatment regimen, the factors significantly associated with low vitamin D were race, season of sampling (winter/spring), high or low body mass index (BMI) and lower HIV viral load.

Analysis that took into account history of previous AIDS-defined illness and controlled for season, baseline CD4 count and viral load, BMI and race showed that low vitamin D concentrations at the start of therapy were associated with a twofold increase in the risk of clinical disease progression (HR = 2.13; 95% CI, 1.09-4.18).

The investigators cite other studies showing it is “biologically plausible” that low vitamin levels would increase the risk of poor clinical outcomes.

Low vitamin D at baseline more than doubled the risk of virological failure (HR = 2.13; 95% CI, 1.81-3.50). The authors note that theirs is the first study to identify vitamin D as a factor in the virological outcomes of therapy.

There was also evidence suggesting that low vitamin D increased the risk of a poor CD4 response to treatment. However, there were too few cases for this to be proved.

“The associations found in this paper raise questions of reverse causation: does advanced HIV disease cause low [vitamin D] concentrations; or, is low [vitamin D] concentration a general marker for poor health,” write the authors. “The fact that this was prospective and that severely ill persons were excluded from the study makes this unlikely. Also, [vitamin D] concentrations were comparable to those found in studies of non-HIV infected persons in similar populations.”

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Review of abstracts from recent conference

By Lucinda Porter
HCV Advocate

Note: These HCV “Snapshots” feature selected abstracts from the May 2014 meeting of Digestive Disease Week. The research presented here came from conference posters and presentations, representing part of a picture. There are multiple factors that influence treatment outcomes such as the number of patients in the study, patient demographics (weight, age, ethnicity), and study design (inclusion criteria, placebo vs. open label, etc.) to name a few. Unless and until these studies are published in peer-reviewed journals, these data and conclusions are considered preliminary.


This study gathered data from medical records and estimated the liver disease stage of 227,563 Veterans Administration patients with chronic hepatitis C infection (HCV). Using these data, they forecasted the outcomes if:

Patients received no treatment (NT)
- Projected deaths in 2014 = 958; 2019 = 1490; 2024 = 1800

Patients were treated with pegylated interferon and ribavirin (PR)
- Projected deaths in 2014 decreased 7.1%; in 2019 decreased 8%; 2024 decreased 8.9%

Patients were treated with pegylated interferon, ribavirin, and a protease inhibitor (PRPI)
- Projected deaths in 2014 decreased 10.9%; in 2019 decreased 12.3%; 2024 decreased 13.7%

Patients were treated with new all oral hepatitis medications expected to be released in 2014, such as sofosbuvir and ledipasvir.
- Projected deaths in 2014 decreased 50.2%; in 2019 decreased 56.7%; 2024 decreased 63.1%

The Bottom Line: Oral hepatitis C therapies are anticipated to save lives, and provide other positive health outcomes.

Editorial Comment: Hepatitis C-related deaths may be under reported. Hepatitis C patients are at increased risk of premature death from other medical conditions such as heart disease, stroke, and cancer. Since these factors are not captured in this analysis, the potential benefits of new hepatitis C treatments may be greater than what is reported here.


There has been a campaign to implement recommendations by the Centers for Disease Control and Prevention to screen baby boomers (those born from 1945-1965) for hepatitis C, hoping to find undiagnosed patients who might otherwise fall through the cracks. It has been estimated that birth year screening will identify 800,000 Baby Boomers with hepatitis C who might not otherwise be diagnosed. However, there isn’t strong data on actual hepatitis C diagnosis in communities. This study, conducted in Olmsted County, Minnesota, looked at blood samples of residents born from 1954 through 1976.

The Bottom Line: The prevalence of hepatitis C in this rural Midwestern was similar to national data, confirming that the majority of those with hepatitis C are not yet diagnosed, including the majority of hepatitis C patients who are younger, between ages 30 and 49.

Editorial Comment: Hepatitis C is a growing problem in our youth, and younger adults. Those who are 30 to 49 may be overlooked. This study emphasizes the need to screen everyone, not just Baby Boomers. In addition to birth year screening, we also need to ramp up risk-based screening.


Of the more than 52,000 participants in the National Household and Nutrition Examination Survey 2001-2010, 502 (1.3%) tested positive for past or current HCV infection. After participants were notified of test results, and encouraged to pursue further care, a follow-up interview was conducted. Approximately 50% of the participants had not known they were HCV+ prior to notification. Roughly 80% pursued medical follow-up.

The Bottom Line: The majority of patients who screen positive for HCV infection do pursue further HCV-related care. Lack of health insurance was the main
"Sustained virologic response is associated with improvement of fatigue," the researchers concluded. "Central fatigue is the type of fatigue primarily affected by HCV clearance. Longer follow-up may be needed to show any potential improvement in peripheral fatigue."

Reference

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patient outcomes, it was not possible to quantify the clinical impact of a PDDI on individual patient health.

Recommendations for patients
Where available, referral to an expert HIV pharmacist for a medication review and assessment of PDDIs is recommended in order to optimize drug treatments.

Patients are highly encouraged to use one pharmacy to fill all of their prescription medications so that drug-drug interactions can be promptly identified.

It is also recommended that patients check with their physician or pharmacist before starting any new prescription medication, over-the-counter drugs, vitamins, supplements, or complementary and alternative medicines to ensure there are no potential drug-drug interactions with their current medication regimen.

Conclusions
Older patients are at a higher risk of experiencing potential drug-drug interactions due to a greater number of non-ARV medications, specifically medications for heart diseases. Increased vigilance should be taken in the care of HIV-positive patients of at least 50 years of age on ARV therapy to prevent drug-drug interactions, to maximize ARV and non-ARV efficacy, and to minimize toxicity.

Reference

Stephanie Lynch, RPh, is a pharmacist and doctoral student of pharmacy at the University of Toronto. She graduated from Dalhousie University with a Bachelor of Science in pharmacy in 2011 and completed an accredited Canadian pharmacy residency program at the Moncton Hospital, Horizon Health Network in 2012.

Alice Tseng, PharmD, is a pharmacist at the Immunodeficiency Clinic, Toronto General Hospital and assistant professor with the faculty of pharmacy, University of Toronto. She is an editor of two popular websites on HIV and hepatitis C drug interaction and pharmacology information—hivclinic.ca and hcvdruginfo.ca. She is also a reviewer of this year’s drug guide.

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The investigators believe their findings support the concept of vitamin D supplementation as an adjunct to HIV therapy, concluding “a well-designed clinical trial is needed.”

Reference

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reason when further medical care was not pursued.

Editorial Comment: The hope here is that health care coverage expansion will increase access to HCV medical care. Also noteworthy is that the median age of the HCV+ participants was 49, which means that quite a few were born after 1965, the limit of the age-based testing recommendation.


This study used data from the 2012 U.S. National Health and Wellness Survey. Of the 71,157 respondents, 0.9% reported chronic HCV, 1.3% reported congestive heart failure (CHF), 2.8% reported myocardial infarction (MI or heart attack), 5% reported chronic obstructive pulmonary disease (COPD), 10.9% reported diabetes, 14.9% reported depression, and 17.3% reported osteoarthritis (OA).

The Bottom Line: Compared to the other six medical conditions, HCV patients were second only to depression in the mental quality of life component of the survey. HCV patients were third on physical quality of life. A quarter of the HCV participants worked full-time, but reported loss of productivity at work and missed work.

Editorial Comment: Although hepatitis C is largely invisible and silent, it has the power to do significant damage.
Hemophilia Association of the Capital Area
2014 Calendar of Events

**July**
- 14 Women’s Support Group and Dinner, The Greene Turtle, Fairfax VA – 6:30 pm
- 31 Deadline for Getting in the Game Applications

**August**
- 4 Men’s Support Group and Dinner, Tutto Bene Restaurant, Arlington, Virginia – 6:30 pm

**September**
- 4 KUWYH Dinner, Transition Children to Independence, Green Turtle Restaurant, Fairfax, VA 6:30 pm. Pfizer presenting.
- 8 Women’s Support Group and Dinner, Location/Time TBD
- 15 Board Meeting, 7:00 pm – Location TBD
- 18-20 NHF Annual Meeting, Washington, DC (HACA is host chapter)
- 20 Annual Membership Meeting – at NHF Annual Meeting
- 24 Infusion Class, Children’s National Health System, Washington, DC – 6:30 pm

**October**
- 2 KUWYH Lunch, Exploring Mental Health in Hemophilia Community, Washington, DC, Location/Time TBD. Pfizer presenting.
- 3 KUWYH Dinner, Partnering with Your School, Washington, DC. Baxter presenting. Followed by DC United Versus Sporting Kansas City, Washington, DC – 8:00 pm
- 4 New Family Luncheon – noon, location TBD
- 6 Men’s Support Group and Dinner, Tutto Bene Restaurant, Arlington, Virginia – 6:30 pm
- 17-19 CSL Behring Getting in the Game, Phoenix, Arizona
- 25 National Hemophilia Walk, Lincoln Memorial, Washington, DC.

**November**
- 3 Women’s Support Group and Dinner, , Location/Time TBD
- 5 KUWYH Dinner, Navigating the Financial Aid and Scholarship Process, Maryland, Location/Time. Biogen Idec presenting.
- 8 Women’s Day Out: Capitol Hill Food Tour
- 15 Career, Education & Opportunities (CEO) Young Adult Program, Location TBD - Washington, DC

**December**
- 1 Men’s Support Group and Dinner, Tutto Bene Restaurant, Arlington, Virginia – 6:30 pm
- 6 Holiday Event

All events are free to HACA members. To join or register for an event, contact us at 703-352-7641 or admin@hacacares.org