Positive News

Information Magazine for people with Hepatitis C and HIV

The Irish Haemophilia Society

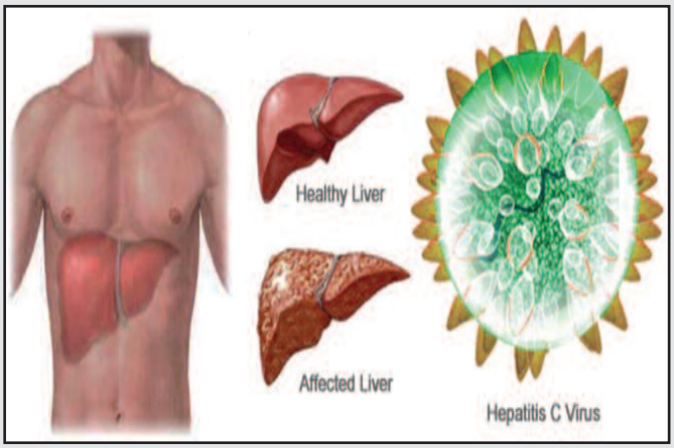
Representing people in Ireland with haemophilia and related bleeding disorders

In this edition of Positive News, there are some articles covering a wide range of topics including:

- An update from the 50th conference of the European Association for the Study of the Liver, (EASL) including highlights from the scientific presentations.
- An update from a European Hepatitis C Conference that took place in Dublin recently.
- An article that looks at the new guidelines, for the roll out of Hepatitis C treatment.
- An article on the different stages of liver damage, and what it means for your liver.
- An update on the current situation, in relation to the roll out of the new treatments.

The article which looks at the highlights, from the scientific presentations from the EASL Conference, includes information on new drugs that are effective against all genotypes, as well as information on treatment for those with advanced liver disease and post-transplant. In the vast majority of cases, people are being cured with these new treatments. However, a small percentage of those treated have failed and at the conference this year some studies looked at re-treating those patients. Another big component at this year's conference was the treatment of patients with renal disease, which could not have been done previously due to the way some treatments are excreted from the body.

Closer to home, the European Conference that took place in Dublin for haemophilia organisations from 27 European countries, was excellent. Speakers at this conference gave a brief overview of the current state of the art treatments available in Europe. Interestingly, speakers spoke about the different levels of access that are available across Europe from no access at all, to access for cirrhotic patients only, to full access. There was also an interesting discussion on preparation for treatment and points that haemophilia organisations need to consider, when talking to patients about the new treatments.



In this magazine, we also look at the topic of liver transplantation. Over the years, we have had some members who have needed a liver transplant. This article looks at the transition from the Hepatology centre to St. Vincent's hospital for liver transplantation. From the initial assessment, to how long it will take, what tests need to be done, why the process is the way it is, why there may be delays, the operation itself and post-transplant. It can be a long process at a frustrating time for many people, but hopefully this article will give a better insight into liver transplantation, particularly for those who may be waiting.

If you have any queries on any of the articles in this magazine, please don't hesitate to contact the Society on 01 6579900. If you are on treatment, and there is something the Society can help you with, please contact us. We are committed to offering practical support and assistance to members on Hepatitis C treatment.

Edition: August 2015

NEW HEPATITIS C TREATMENTS: ACCESS AND ROLLOUT UPDATES

As of January 2015, there are currently six drugs that are available for the treatment of Hepatitis C either on they're own or in combination with other licensed drugs. These are:

- Sovaldi ® (Sofosbuvir)
- Olysio ® (Simeprevir)
- Daklinza® (Daclatasvir)
- Harvoni® (Sofosbuvir / Ledipasvir)
- Vierkirax® (Ombitasvir /Paritaprevir /Ritonavir)
- Exviera® (Dasabuvir)

These drugs once licensed are assessed by the National Centre for Pharmacoeconomics (NCPE) for cost-effectiveness. A summary of the current assessment recommendations are listed here, and more details are available on the NCPE website (www.ncpe.ie). There are still some assessments that are being finalised and are due shortly.

In November 2014, the early access programme was announced and rolled out to approximately 120 patients who were deemed to have an urgent need for treatment. The patients were chosen by two main criteria which effectively narrowed patients to those who were at significant risk of death, or irreversible liver damage, within the next 6 - 12 months. Patients chosen had a one-year mortality rate of between 45-80%.

The commencement of this programme started in early December and by the end of March 2015, over 80 patients were finished treatment under this programme. Of the patients who received the treatment, 95% have been found to have no evidence of the Hepatitis C virus in their blood at the end of treatment and were then awaiting their final results in late June. There were also a number of patient's still under-going treatment. The

cost for the twelve-week course treatment, quoted at the time, was between €45,000 and €55,000.

Through discussions with clinicians and patient groups and realising the need to treat those who were moving towards the first two criteria, and to prevent it, the Health Service Executive (HSE) allocated €30 million in the 2015 primary care budget for the treatment of Hepatitis C. In May of this year, the HSE, through the Irish Hepatitis C Outcomes Registry Network (ICORN), started rolling out the next phase of treatment of those where cirrhosis has begun. This is based on clinical need and patients are currently being identified through the Hepatology centres and infectious diseases centres. The funding that is currently available, based on the prices for the treatments above, should allow all patients with cirrhosis to be treated before the end of the year and potentially a few patients with late stage fibrosis who have accelerating factors such as HIV or HBV co-infection or those with liver transplants. Further roll out will then continue to treat patients with fibrosis, while also treating anyone who presents in clinics with cirrhosis. Like many countries in Europe, the aim is to work back through those with Hepatitis C and treat those who are progressing the fastest.

ASSESSMENT RECOMMENDATIONS

Product	Interferon	Licenced	Commenced	Rapid Review Completed	Full Evaluation Completed	Summary Response
Olysio	With	Mar 2014	May 2014	July 2014	Not Required	Full pharmacoeconomic assessment not recommended when used in triple therapy with peg-interferon and ribavirin.
Sovaldi	With	Dec 2013	Feb 2014	Mar 2014	Oct 2014	Reimbursement Recommended for certain subgroups
Olysio with Sovaldi	Without	NA	May 2014	July 2014	March 2015	Reimbursement recommended in some subgroups
Daklinza	With /Without	Aug 2014	Aug 2014	Sept 2014	May 2015	Reimbursement recommended for certain subgroups
Harvoni	Without	Dec 2014	Nov 2014	Dec 2014	On-going	
Vierkirax	Without	Jan 2015	Dec 2014	Jan 2015	On-going	
Exviera	Without	Jan 2015	Dec 2014	Jan 2015	On-going	

LIVER DAMAGE: THE STAGES OF PROGRESSION

Talking about liver disease, knowing what the terms are and the current situation of your liver's health is very important. Sometimes just being aware of the words and phrases used can help you not to get lost in the conversation, so this is a quick synopsis of the stages of liver disease.

Like other liver conditions, Hepatitis C progresses in stages. The usual progression is from inflammation to fibrosis to cirrhosis. Cirrhosis can progress to end-stage liver disease and can give rise to liver cancer. There are many scales used to quantify the level of fibrosis or cirrhosis and the most commonly used scale in Ireland, is the Metavir scale, which goes from F0 to F4. While it is difficult to categorise exactly, this may give you some idea of what the various scores mean, as you go through the article.

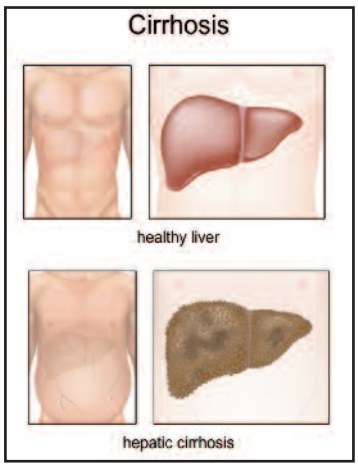
Inflammation

Liver inflammation refers to the presence of special cells called inflammatory cells in the liver. Chronic inflammation is inflammation that persists over a long period. It leads to changes in the liver structure, slower blood circulation, and the death of liver cells (necrosis). Chronic inflammation eventually causes scar tissue to form, which is known as fibrosis. By controlling liver inflammation, you can control the progression to fibrosis. This is done by reducing alcohol intake, eating healthily and having a healthy lifestyle. In this case, the score would range from F0, which is no scarring, to F1, which is minimal scarring.

Fibrosis

Fibrosis is scar tissue that forms as a result of chronic inflammation and extensive liver cell death. The amount of fibrosis in your liver is one way of evaluating how quickly Hepatitis C appears to be progressing. Having knowledge of approximately when you were initially infected, is most useful in determining your rate of disease progression. Liver fibrosis does not occur at the same rate in all individuals and in some people fibrosis remains stable, or may even regress, over time. Several factors influence fibrosis progression. Fibrosis occurs more rapidly in men than in women, and also in older people, particularly those over 50 years of age. Progression does not seem to be linear; that is, the process appears to accelerate as more damage occurs. Also patients with HIV coinfection or those on immunosuppressive drugs after a liver transplant, it has been shown that fibrosis accelerates. Heavy alcohol consumption is strongly associated with worsening fibrosis and cirrhosis. Studies indicate that fatty liver (steatosis) and insulin resistance are associated with more rapid and severe fibrosis. In contrast, viral load (how many copies of the virus you have in your body) does not appear to have much effect on fibrosis progression. With genotype

3 the rate of fibrosis, cirrhosis and liver cancer increases when compared to genotype 1. Genotype 2 appears to have a lower risk of disease progression than genotype 1. In the early stages of fibrosis, the liver functions relatively well (F1 moving to F2 and early F3 on the scale) and few people experience symptoms. However, as the inflammation and liver injury continue, scar tissue builds up and connects with existing scar tissue (F3 on the scale), which can eventually disrupt the way the liver works. It was once thought that fibrosis was irreversible, but research has shown that treatment for Hepatitis C can slow or stop fibrosis progression, and potentially even reverse existing liver damage.



Cirrhosis

When fibrosis becomes widespread and has progressed to the point where the liver has become abnormal, fibrosis has progressed to cirrhosis (F4 on the scale). Cirrhosis is the result of long-term liver damage. Cirrhosis is accompanied by a reduction in blood supply to the liver. The loss of healthy liver tissue and the reduced blood supply can lead to abnormalities in liver function. Even when liver disease has progressed to cirrhosis, it may still be possible for the damage to be at least partially reversed if the Hepatitis C virus is removed. Cirrhosis progression is usually slowed down or even stopped after treatment.

The onset of cirrhosis is usually silent, with few specific symptoms to identify this development in the liver. As scarring (fibrosis) and cell death continues, some of the following signs and symptoms may occur: loss of appetite, nausea and/or vomiting, weight loss, change in liver size, gallstones, itching, and jaundice. However, a large number of people live many, many years with cirrhosis, without any decompensation or symptoms.

It is important to note that once cirrhosis develops, it is critical to avoid further progression of the disease. People with cirrhosis should completely avoid the consumption of alcohol in any form. Once a person has cirrhosis, they are then further categorised to see where they are at. One of the most common classifications is called a Child-Turcotte-Pugh (CTP) score.

There are three stages of cirrhosis:

- Stage A ("compensated"; not too sick)
- Stage B (beginning to decompensate; complications beginning to appear)
- Stage C ("decompensated"; end stage)

The CTP Score is based on five questions. You receive a point value (score) for each of the answers.

Here's how it works:

1. Blood Test - Total Serum Bilirubin

Bilirubin is <2 mg/dl -	1 point
Bilirubin is 2-3 mg/dl -	2 points
Bilirubin is >3 mg/dl -	3 points

2. Blood Test - Serum Albumin

Albumin is >3.5 g/dl -	1 point
Albumin is 2.8 to 3.5 g/dl -	2 points
Albumin is <2.8 g/dl -	3 points

3. Calculation based on a blood test - INR

INR is <1.70-	1 point
INR is 1.71 to 2.20-	2 points
INR is >2.20-	3 points

4. Ascites

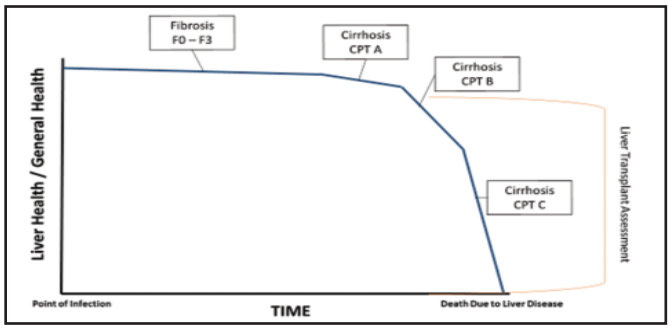
No Ascites -	1 point
Ascites controlled medically	2 points
Ascites poorly controlled	3 points

5. Encephalopathy

No Encephalopathy	1 point
Encephalopathy controlled medically	2 points
Encephalopathy poorly controlled	3 points

Total your score.
Total sum score gives grades of:
5 to 6 points = Stage A Cirrhosis
7 to 9 points = Stage B Cirrhosis
10 to 15 points = Stage C Cirrhosis

Usually, a person has to be at least stage B or stage C, to get referred for an "Assessment" to go on the liver transplant waiting list.



EASL: EUROPEAN RECOMMENDATIONS AND GUIDELINES

During the 50th International Liver Congress, hosted by the European Association of the Liver (EASL) conference in Austria, a new set of recommendations were outlined for the diagnosis and treatment of Hepatitis C (HCV) for 2015. The guidelines recommend a variety of Interferon-free Direct Acting in Antivirals (DAA's) regimens for people with Hepatitis C virus genotypes 1 to 6. The guidelines are published online and available on the EASL website, are intended to assist physicians and other healthcare providers, as well as people with Hepatitis C and other interested individuals, in clinical decision-making. The new recommendations apply to therapies that have been approved in the European Union. Hepatitis C therapy has been a rapidly moving field but in general things are stabilising with overall SVR rates above 90%. The next step going forward is dealing with small sub-groups of people such as those with decompensated cirrhosis, liver transplant recipients, and patients with chronic kidney disease.

Who should be treated?

According to the guidelines, the goal of Hepatitis C treatment is to eradicate the virus in order to prevent liver cirrhosis, decompensation, hepatocellular carcinoma (liver cancer / HCC) and death.

All treatment-naive and treatment-experienced patients with compensated or decompensated cirrhosis, who are willing to be treated and who have no contraindications to treatment, should be considered for treatment. However, as not every patient can be treated within the next year or so, prioritisation is necessary.

The guidelines assign treatment priority based on how much liver damage is current, how fast the damage is progressing, other issues outside the liver that can speed up progression as well as the likelihood of transmitting Hepatitis C. Treatment is a priority for people with advanced fibrosis or cirrhosis including people with decompensated cirrhosis where the liver is unable to continue doing the functions it needs to. However, people with very advanced liver disease may not benefit as much, and alternative options need to considered.

Other high-priority groups include people with HIV or Hepatitis B virus co-infection, people who are awaiting or have received a liver transplant and those with debilitating fatigue. Treatment is also being prioritised for people at increased risk for onward transmission of Hepatitis C, including people who are currently injecting drugs, gay and bisexual men with high-risk sexual practices and women who wish to get pregnant.

The guidelines state that treatment is justified for people with moderate fibrosis. People with no or mild fibrosis are being suggested as able to be deferred from treatment for the moment, but should regularly be assessed for disease progression and to discuss new treatment options that may become available or affordable.

Recommended Regimens by Genotype

Interferon-free Direct Acting Antiviral's (DAA's) regimens are the best options available, due to their efficacy, ease of use and excellent tolerability. This is the case for almost all people whether they are HIV co-infected or mono-infected, or for those who do not have cirrhosis as well as people with compensated or decompensated cirrhosis.

Ribavirin still has a role to play in helping prevent relapse in people with more difficult to treat types of Hepatitis C. The guidelines recommend that people with cirrhosis and liver transplant recipients should include Ribavirin in their Interferon-free regimen, if possible. For those who cannot

use Ribavirin due to intolerance or contraindications, treatment duration should be extended.

In 2014, there were three DAA's available for use and as of January this year three more options have been approved.

Product	Brand Name	Dose	Company
Peg-Interferon		Once weekly injection	
Ribavirin (RBV)		2-3 tablets twice daily	
Sofosbuvir (Sof)	Sovaldi	One tablet once daily	Gilead
Simeprevir (Sim)	Olysio	One tablet once daily	Janssen
Daclatasvir (Dac)	Daklinza	One tablet once daily	BMS
Sofosbuvir / Ledipasvir	Harvoni	One tablet once daily	Gilead
Paritaprevir / Ombitasvir / Ritonavir	Viekirax	Two tablets once daily	Abbvie
Dasabuvir	Exviera	One tablet twice daily	Abbvie

Table 1: Approved HCV drugs in the European Union in 2015

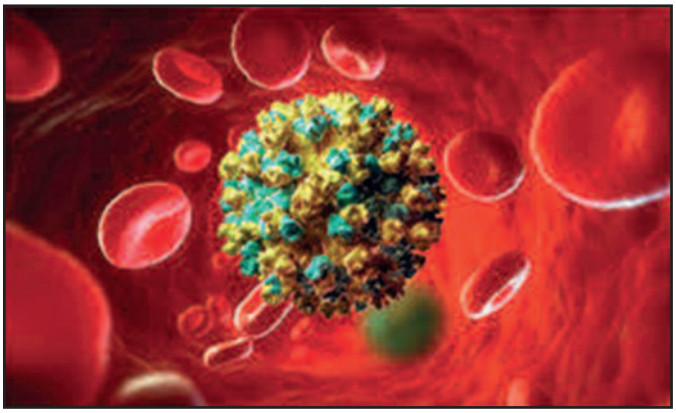
The following regimens are included in the new guidelines, along with the genotypes for which they are indicated:

	Regimen	Genotypes
Interferon-free	Sofosbuvir + ribavirin	2 and 3
	Sofosbuvir/ledipasvir +/- ribavirin	1, 4, 5, and 6
	Paritaprevir/ritonavir/ombitasvir + dasabuvir +/- ribavirin	1
	Sofosbuvir + simeprevir +/- ribavirin	1 and 4
	Sofosbuvir + daclatasvir +/- ribavirin	All
	Paritaprevir/ritonavir/ombitasvir +/- ribavirin	4
Interferon-containing	PIFN(Peg-Interferon) + ribavirin + sofosbuvir	All

Table 2: Regimens included in the new guidelines

The standard duration of Interferon-free therapy is generally 12 weeks. Some people with genotype 1 and without cirrhosis can take Sofosbuvir/Ledipasvir for just eight weeks without Ribavirin. People with genotype 1 who have cirrhosis should add Ribavirin or extend treatment to 24 weeks. Although HCV subtype 1a is considered harder to treat than 1b, treatment recommendations are generally similar.

There are still not many options for people with genotypes 2 or 3. Across genotypes, only a few regimens are recommended for people with decompensated cirrhosis: Sofosbuvir plus Ribavirin (genotype 2 and 3), and Sofosbuvir with either Ledipasvir (genotypes 1 and 4) or Daclatasvir (all genotypes).



Other Considerations

In addition to specific antiviral regimens, the guidelines also include recommendations on monitoring during treatment, managing side-effects and drug-drug interactions, improving adherence and options for re-treatment of non-responders.

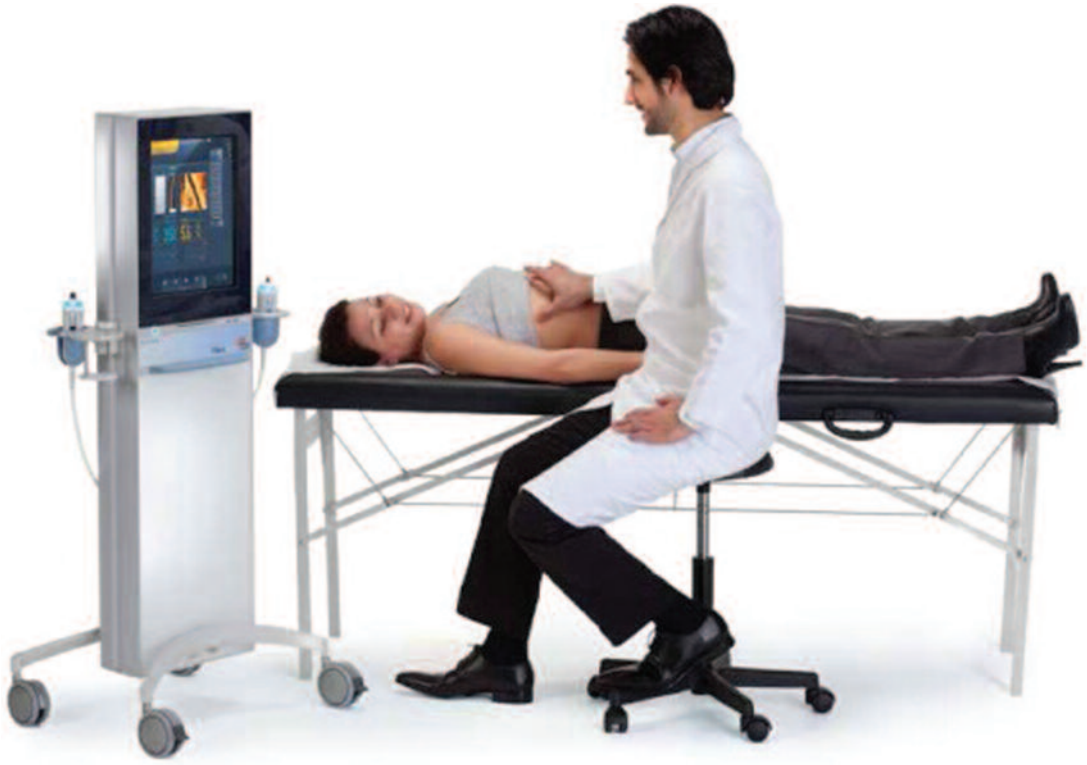
Re-treatment is largely dependent on what regimen a person received initially and whether they carry drug-resistant viral variants.

For people starting treatment for the first time, it was suggested it may be advantageous to "slightly over-treat" with first-line therapy to avoid the need for re-treatment. Unlike the previous treatments, using monitoring during and after treatment at the moment does not help in making decisions about treatment response with DAA's. Generally the response is that viral load goes down fast which is good however it does not predict a cure.

Indications for treating people with HIV co-infection are identical to mono-infected except for the precautions required when taking into account drug-drug interactions with antiretroviral therapy. Changing someone's current HIV medications may not be necessary and in some cases a dose reduction of current anti-retroviral may be all that is needed for the duration of treatment. Looking at people who are on the waiting list for transplant or have received one, treatment recommendations are not as definitive, and there are lots of uncertainties. In general, treatment is recommended before transplant to prevent re-infection of the donor liver graft. However, beyond a certain point it may be better to wait until after transplant and then start treatment once they have their new functional liver.

Non-Invasive Liver Disease Assessment

In addition to the Hepatitis C treatment guidelines, EASL has published joint clinical practice guidelines for non-invasive tests for the evaluation of liver disease severity and prognosis. Traditionally, liver biopsy has been the gold standard for assessing liver injury, and staging was important for deciding which individuals to treat for Hepatitis C. Today, non-invasive methods using various



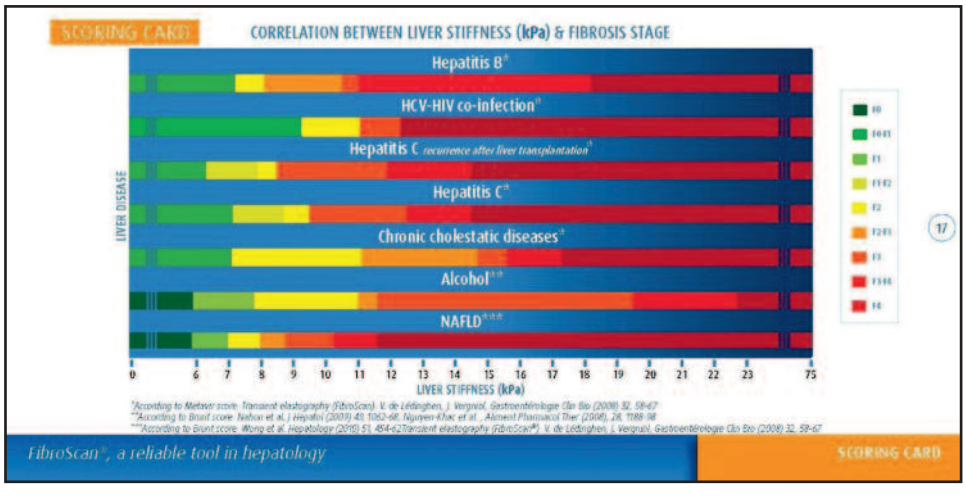
biomarkers and imaging techniques including transient elastography, (FibroScan) are more widely used.

Measurement of liver stiffness is becoming the standard. However, as the Hepatitis C treatment guidelines state both liver stiffness measurement and biomarkers perform well in the identification of cirrhosis or no fibrosis, but they perform less well in resolving intermediate degrees of fibrosis. Furthermore, given the effectiveness and ease of Interferon-free treatment, staging may be less important, as many experts think everyone with Hepatitis C should be eligible for treatment.

Where are the Gaps?

The remaining questions include what are the best regimens for people with decompensated cirrhosis, especially those with the most severe form of cirrhosis. There are questions about the optimal timing of treatment pre- or post-transplant as well as better options for people with genotype 3 and renal disease.

In reality, access is the biggest issue now as currently the pricing of these drugs is expensive. In most European countries treatment is limited to patients with cirrhosis. Working coherently at national level would allow better organisation of care and access to treatment and potentially lower prices.



After the barrage of information from the European Association for the Study of the Liver (EASL) conference in London in 2014, the 50th International Liver Congress in Vienna, again provided great information on the advancements of Hepatitis C treatments. Whilst it is a little early to see a large amount of real-world data, based on the timing of the licensing of the recent regimens, some of the highlights of the conference this year focused on results for key topics such as: pangenotypic drugs, the durations of treatment, treating hard to treat patients, re-treating patients who have failed on the new Direct Acting Antiviral's (DAA's) treatments and some focus on patients with Hepatitis C and renal disease.

GENOTYPES 1, 4, 6

Phase 3 Trials

The next to the market is Merck Sharpe and Dohme (MSD) with the combination of a Grazoprevir and Elbasvir. Five trials were presented over the course of the conference.

The C-EDGE programme trials examined Grazoprevir and Elbasvir (with and without Ribavirin) in 420 patients with genotypes 1, 4 and 6 in three main groups:

- C-EDGE TN in treatment-naïve patients
- C-EDGE CO-INFXN in patients with HCV/HIV co-Infection
- C-EDGE TE in treatment-experienced (prior peg-Interferon/Ribavirin treatment failures)

The 218 HIV co-infected patients, were either on stable antiretroviral therapy (ART's) or previously untreated with ART's. ART treatments used in the trial were Raltegravir, Dolutegravir or Rilpivirine, paired with Tenofovir/Emtricitabine or Abacavir/Lamivudine. Other regimens were excluded owing to the potential for drug-drug interactions.

The C-SALVAGE study was designed to investigate the efficacy of Grazoprevir and Elbasvir in people with genotype 1, who had failed to achieve a cure after a previous course of treatment containing peg-interferon and another Protease Inhibitor (PI), either Telaprevir, Boceprevir or Simeprevir. The study excluded patients with decompensated cirrhosis or hepatocellular carcinoma (liver cancer), and people with HIV and Hepatitis C co-infection.

The C-SALT study was designed to evaluate the regimen of Grazoprevir and Elbasvir without Ribavirin in people with genotypes 1, 4 or 6 infection. The study population was restricted to people with Child-Pugh B cirrhosis.

Hepatitis C can increase the progression of kidney disease. However, available treatments have been unsuitable for people with kidney disease. The C-SURFER study recruited people with genotype 1 who had chronic kidney disease. Three-quarters of patients were dependent on dialysis. (As per the table on next page)

GENOTYPES 1, 3

The C-SWIFT study enrolled 102 genotype 1 patients and 41 genotype 3 treatment-naïve patients with and without cirrhosis. Genotype 1 non-cirrhotic (n = 61) patients were randomised to 4 or 6-week durations. Genotype 1 cirrhotic (n = 41) patients were randomised to 6 or 8 weeks of therapy. Genotype 3 non-cirrhotic patients (n = 29) were randomised to 8 or 12 weeks and genotype 3 cirrhotic patients (n = 12) were assigned to 12 weeks of therapy. All patients received the same regimen of Grazoprevir and Elbasvir with Sofosbuvir.

The results from all the C- studies are summarised in the table below.

Trial	N	Patient type	GT	Cirrhosis	Rx duration (wk)				RBV	SVR		
										Overall	GT 1a	GT 1b
GZR/EBR±RBV												
C-EDGE TN	420	Naive	1,4,6	22%			**12**		-	95%	92%	99%
C-EDGE TE	420	Experienced	1,4,6	35%			**12**	**16**	+ -	94%	95%	99%
C-EDGE CO-INFXN	218	HIV/HCV	1,4	16%			**12**		-	95%	94%	95.5%
C-SALVAGE	79	PI-failure	1	43%			**12**		+	96%	93%	98%
C-SALT Low-dose GZR	30	CPT B	1	100%			**12**		-	90%	89%	100%
C-SURFER	235	Kidney Disease	1	6%			**12**		-	94%	N/A	N/A
SOF + GZR/EBR												
C-SWIFT	142	Naïve and Experienced	1,3	NC/CC	**4**	**6**	**8**	**12**		-	**GT 1**	**GT 3**

GENOTYPE 1

Another study RUBY I, examined the Abbvie 3-D regimen in non-cirrhotic genotype 1 patients with chronic kidney disease. Patients with genotype 1a received additional low dose Ribavirin whereas patients with genotype 1b were treated without Ribavirin. In this ongoing trial, 20 patients were included, 14/20 completed 12 weeks of 3-D with and without Ribavirin so far, and all were clear of the virus at the end of treatment, with 2 patients 12 weeks post treatment and their sustained viral response (SVR) rate of 100%. As most patients have not yet reached post-treatment week 12, conclusions on efficacy are limited. Nevertheless, to date all patients completing treatment had a good response.

ALL GENOTYPES

In the ALLY-1 trial, which examined Sofosbuvir and Daclatasvir with Ribavirin for 12 weeks, 60 people with advanced liver cirrhosis and 53 people post liver transplantation were enrolled. About 60% had been treated previously. Overall, 83% of the people with advanced cirrhosis and 94% of the post-transplant patients achieved a sustained virological response 12 weeks after treatment (SVR12). Looking just at the people with genotype 1, the corresponding cure rates were 82% and 95% and the 12/13 people who did not achieve a sustained viral response after 12 weeks (SVR12) relapsed after the end of treatment. People who relapsed are now being re-treated with the same regimen for 24 weeks.

Looking at those with advanced cirrhosis by genotype, the SVR12 rates were 76% for subtype 1a, 100% for 1b, 80% for genotype 2, 83% for genotype 3 and 100% for genotype 4. In the post-transplant cohort, the response rates were consistently high: 97% for 1a, 90% for 1b and 91% for genotype 3. Looking at other factors associated with response in the cirrhosis cohort, SVR12 rates were 92% and 94% for Childs-Pugh Class A and B but fell to 56% for Class C.

The most common adverse side effects were headache, fatigue, anaemia, diarrhoea and nausea. One person with cirrhosis and one transplant recipient stopped all treatment due to adverse side effects, but both nonetheless achieved an SVR12. Transplant recipients did not require modification of their immunosuppressant regimen, due to drug interactions and there were no cases of graft rejection or hepatic decompensation.

GENOTYPES 2, 3

The advent of Direct Acting Antiviral agents has brought about a revolution in treatment for Hepatitis C. However, people with genotype 3 do not respond as well to available Interferon-free regimens, and those with liver cirrhosis and non-responders to prior therapy are particularly in need of more effective treatment options. The BOSON study went back and explored Sofosbuvir with peg-Interferon and Ribavirin for 12 weeks against Sofosbuvir, with Ribavirin for 16 or 24 weeks in treatment-experienced genotype 2 patients with cirrhosis, and in treatment-naïve and experienced genotype 3 infected patients with and without cirrhosis.

In the hard-to-treat genotype 2 patients, SVR12 rates were 87% for Sofosbuvir plus Ribavirin for 16 weeks, 100% for the dual regimen for 24 weeks, and 94% for Sofosbuvir plus Ribavirin with pegylated Interferon for 12 weeks.

However, in the larger group of patients with genotype 3, SVR rates were 71% for Sofosbuvir plus Ribavirin for 16 weeks and 84% for 24 weeks, but rose to 93% for Sofosbuvir plus Ribavirin with peg Interferon – the highest cure rate observed to date for this population in a phase 3 study. Within the genotype 3 group, SVR12 rates were 80% for 16 weeks, 87% for 24 weeks and 95% for 12 weeks with Interferon, for people without cirrhosis. The most dramatic improvement in response was seen for people with cirrhosis: 51% for 16 weeks, 79% for 24 weeks and 88% for 12 weeks with Interferon. Among previously untreated patients, SVR12 rates were 77%, 88% and 95%, respectively. A big improvement was also seen when adding Interferon for treatment-experienced patients: 64%, 80% and 91%, respectively. Focusing on the "toughest of the tough" group, genotype 3 prior non-responders with cirrhosis – the cure rate rose from just 47% for 16 weeks to 86% for the Interferon-containing regimen taken for 12 weeks. While most people with Hepatitis C and health professionals want to avoid Interferon-containing therapy in the direct-acting antiviral era, in certain circumstances Interferon may still have a role to play for certain groups.

GENOTYPE 1

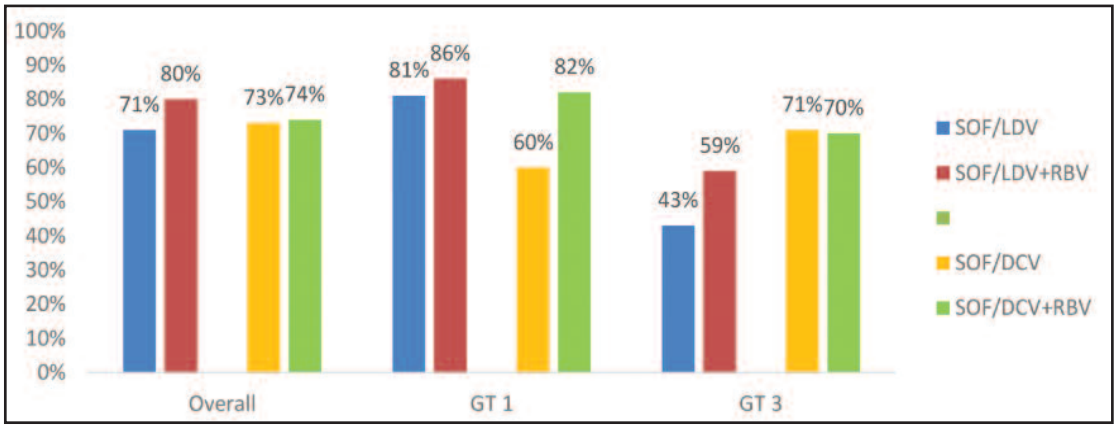
In one very interesting study, re-treating with Sofosbuvir and Ledipasvir without Ribavirin was evaluated in patients who had failed on other trials. Most had previously used Sofosbuvir and Ledipasvir with or without Ribavirin while eight had used Sofosbuvir and Ledipasvir plus another experimental drug.

All were re-treated with Sofosbuvir/Ledipasvir without Ribavirin, for 24 weeks. Not surprisingly, given their prior treatment failure, this is a challenging population, 46% had liver cirrhosis and almost 75% had been previously treated for 8 weeks and the rest for 12 weeks. This result was an overall SVR12 rate of 71%. There was not much difference in the response between people with and without cirrhosis (68% versus 74% respectively). However, people initially treated for 8 rather than 12 weeks had a substantially higher SVR12 rate: 80% versus 46%, respectively. In one person, the virus rebounded while on treatment, and the other 11 relapsed, usually between the end of therapy and 4 weeks post-treatment.

GENOTYPE 1, 3

Real World

Interesting, data on the NHS English Early Access Programme (EAP) was also presented. This programme provided 12 weeks of therapy with Sofosbuvir, with or without Ribavirin and an NS5A inhibitor (Ledipasvir or Daclatasvir) to a cohort of patients with decompensated cirrhosis. In this analysis, information on 467 patients (235 with genotype 1, 189 with genotype 3) was presented, with 47% being treatment experienced, 10% were liver transplanted and 5.7% were HIV co-infected. This was a group of patients with very advanced liver disease, 94.4% either had decompensated cirrhosis or a history of decompensated cirrhosis. Of the group 66.2% were classified as CPT B and 9.9% as CPT C and 38.1%, had active ascites and 17.1% active encephalopathy. The SVR12 rates obtained so far in this ongoing study are shown below.



In patients with decompensated cirrhosis, 12 weeks therapy, with Sofosbuvir, plus an NS5A inhibitor, is effective with most patients achieving an SVR12. Patients with genotype 1, respond well with >80% achieving SVR12 and response rates were slightly reduced in patients with genotype 3. Although numbers are small, it appears as if more patients achieve an SVR12 with the combination Sofosbuvir and Daclatasvir rather than Sofosbuvir and Ledipasvir, respectively. This would make sense as the in vitro data suggests there is more activity against genotype 3 for Daclatasvir than Ledipasvir. It has been noted that this may be a sub optimal treatment duration and with a maximum of 71% responding to genotype 3 therapies. Obviously the question becomes whether extending the duration to 24 weeks could further improve success rates in this challenging patient population with very advanced cirrhosis stages.

GENOTYPE 1

Another interesting study examined the real-world effectiveness of Sofosbuvir and Ledipasvir for 8 weeks of treatment of genotype 1 and 4 in 45 patients. The 8-week treatment included treatment naïve patients, with a viral load of less than 6 million and none to bridging fibrosis. In 41 of the 43 patients who were finished treatment and beyond the first 4 weeks, the success rate was 100%. However, the numbers are still small, and results are still early in this study.

GENOTYPE 1, 4

PHASE 2 Trials

In the SOLAR-2 trial, it evaluated Sofosbuvir, Ledipasvir and Ribavirin in people with advanced liver disease. This phase 2 study enrolled more than 300 people with Hepatitis C. Most had genotype 1 while about 10% had genotype 4. About 80% had received prior treatment with 160 people having decompensated cirrhosis who were either awaiting or had received liver transplants. They were classified as Child-Pugh-Turcotte (CPT) class B or C. The study also included 168 liver transplant recipients with CPT Class A cirrhosis and without cirrhosis.

Preliminary results showed that the CPT B/C patients had SVR12 rates of 85% with 12 weeks of treatment and 88% by 24 weeks. In the CPT A group, SVR12 rates were 95% and 98%, respectively. The overall cure rates were similar for 12 and 24 weeks of therapy. Patients with CPT B responded somewhat better than those with CPT C, and within the CPT C group pre-transplant patients did better than post-transplant patients.

GENOTYPE 1, 4

The SVR was also associated with improved liver function. Almost all CPT A patients remained the same with 35% of those initially classified as class B reverted to class A, while 48% of those classified as class C reverted to class B and 5% to class A. Given that this was a population with advanced disease, almost all patients experienced some adverse events. Twelve patients died during the study – mostly due to liver-related complications – but no deaths were considered treatment-related. Six people discontinued treatment due to adverse events, all but one of whom had decompensated cirrhosis. The most common adverse events were fatigue, anaemia, nausea and headache.

ALL GENOTYPES

Now that Interferon-free Direct-Acting Antiviral's (DAA's) regimens taken for 12 weeks can cure most people with genotype 1, researchers are working to develop new drugs that work against multiple Hepatitis C genotypes (known as 'pan-genotypic'). This can produce a sustained viral response (SVR or cure) with a shorter duration of treatment, which would be more convenient for patients and could potentially lower costs.

In preclinical and early clinical research presented at EASL, GS-9857 demonstrated activity against all genotypes and an improved resistance profile. As a result, this is being added to a single tablet combination of Sofosbuvir and GS-5816 (being called Velpatasvir) which is further along the pipeline in Phase 3 ASTRAL trials. The combination of all three drugs are being tested in a Phase 2 study which enrolled 75 people with genotype 1. Previously untreated patients without cirrhosis were randomly assigned to receive all 3 drugs for 4 or 6 weeks. Treatment-naive patients with cirrhosis, and treatment-experienced patients (including 17% with cirrhosis) who were not previously cured with Interferon-free regimens, all received the triple regimen for 6 weeks.

In those on the 6-week regimen, 93% of treatment-naive patients without cirrhosis achieved an SVR after 12 weeks (SVR12). The SVR12 rate was 87%, of treatment-naive patients with cirrhosis but fell to 67% for treatment-experienced patients. Within the treatment-experienced group, cure rates were 68% for people without cirrhosis and 60% for cirrhotic, but the latter subgroup included only five patients.

The 4-week treatment duration did not perform as well with an SVR12 rate of only 27%. In all cases where the treatment did not work, this was due to relapse after the end of treatment. Patients who had been previously treated with Sofosbuvir and Ledipasvir for 12 weeks had an SVR12 rate of 46% compared to those who had been previously treated for 8 weeks.

Everyone completed treatment, and there were no serious adverse events or drug discontinuations for this reason. The most common side-effects were nausea (25%), headache (24%) and fatigue (16%). Four people (5%) experienced transient, asymptomatic lipase elevations.

Ongoing phase 2 studies are now testing Sofosbuvir/GS-5816 plus GS-9857 for all genotypes for treatment durations of 6, 8 and 12 weeks in treatment-naive and treatment-experienced cirrhotic and non-cirrhotic patients.

GENOTYPE 1

Preliminary results from a Phase 2b study (n=79) of ABT-493 and ABT-530 in non-cirrhotic genotype 1 patients, receiving the Ribavirin free recommended regimen for 12 weeks, demonstrated a sustained virologic response rate at four weeks post-treatment (SVR4) of 99 percent (n=78/79).

A further study also addressed shorter treatment durations with new DAA's from Achillion. This Phase 2 study looked at ACH-3102 and Sofosbuvir. The study population was a treatment naïve, genotype 1, non-cirrhotic patient group. Overall 6 and 8 weeks, each with 12 patients, were studied. An SVR12 was achieved in 100% of all patients. Therefore, this becomes the first study to report 100% SVR12 in patients using a two-drug combination for 6 weeks.

EUROPEAN HEPATITIS C CONFERENCE

From the 5th - 7th of June 2015, a European Hepatitis C Conference was organised in Dublin by the Irish Haemophilia Society, to assist in the transfer of knowledge with the new Hepatitis C treatments. Current access levels within each country and aspects of advocacy used in each country was also on the agenda. Over 40 delegates from 21 countries arrived on Friday evening. A brief introduction gave some tips on how to spot the difference in how the drugs work by looking at the names and what they end in. For example: Previr means Protease Inhibitors, Buvir means Non-Nucleoside or Nucleoside Inhibitors and Asvir meaning NS5A Inhibitors.

Brian O'Mahony, Chief Executive, I.H.S.

On Saturday, Brian O'Mahony presented an overview on Hepatitis C and haemophilia in Europe. In a survey of 29 countries, there are over 11,000 people with bleeding disorders in Europe who have Hepatitis C. A further 19 countries were not accounted for as they did not respond to the survey. Professor of Haemostasis & Thrombosis Mike Makris followed up with some interesting points based on one centre's experience. In the Sheffield Haemophilia Treatment Centre, a look back showed anyone treated before 1985 with haemophilia treatment was positive for Hepatitis C. This was due to patients being exposed (through their haemophilia treatment) to large plasma pools, over a 10 year period, with up to 2 treatments per week. In this case, it led to an individual being exposed to 26 million donations of plasma. After 1985, the transmission dropped significantly due to viral inactivation of haemophilia treatment products. Furthermore, he pointed out that in the EUHASS (European Haemophilia Safety Surveillance) project, the biggest cause of mortality and adverse events (generally liver cancer) in people with haemophilia across Europe since 2008, has been directly as a result of Hepatitis C. This set the focus (not that it was needed) for the weekend.

Dr. Diarmuid Houlihan, Hepatologist gave a presentation on the clinical progression of Hepatitis C and the importance of treating.

Dr. Diarmuid Houlihan, Hepatologist, St. Vincent's Hospital.

He spoke about the complications of end-stage liver disease which develops during cirrhosis such as varices, ascites (fluid on the abdomen) and encephalopathy, all of which can cause a lot of problems for patients during this stage of Hepatitis C. In a number of cases, patients with Hepatitis C can also develop hepatocellular carcinoma (HCC or liver cancer) which requires treatment either through surgery, resection or transplantation. Methods such as thermal ablation or chemotherapy can be used in the interim. These slow down the progression of the liver cancer in order for the patient to gain time to wait for a liver transplant.

In Ireland in 2014, 34 patients required a liver transplant directly as a result of Hepatitis C. Over the last 20 years the overall survival rates post liver transplant at 1, 3 and 5 years are 92%, 86% and 78% respectively. However, this changes quite dramatically when Hepatitis C is the cause for the liver transplant. Survival rates reduce at 1, 3 and 5 years to 93%, 79% and 67% respectively. This is quite often due to the re-infection of the new liver with Hepatitis C and in some cases it re-infects and aggressively attacks the liver, reducing the survival rates over time.

He also pointed out the significant cost implications of Hepatitis C on the Irish healthcare system for not treating patients with Hepatitis C (see table below). Of particular interest was the cost for those who may need a liver transplant, which is €137,176.

Hepatitis C Health State	Mean Annual Cost (€)
Mild	398
Moderate	417
Compensated Cirrhosis	1,790
Decompensated Cirrhosis	6,081
Hepatocellular Carcinoma (Liver Cancer)	24, 723
Transplantation Year 1	137,176
Transplantation After Year 1	5,337
Sustained Virological Response (cure)	83

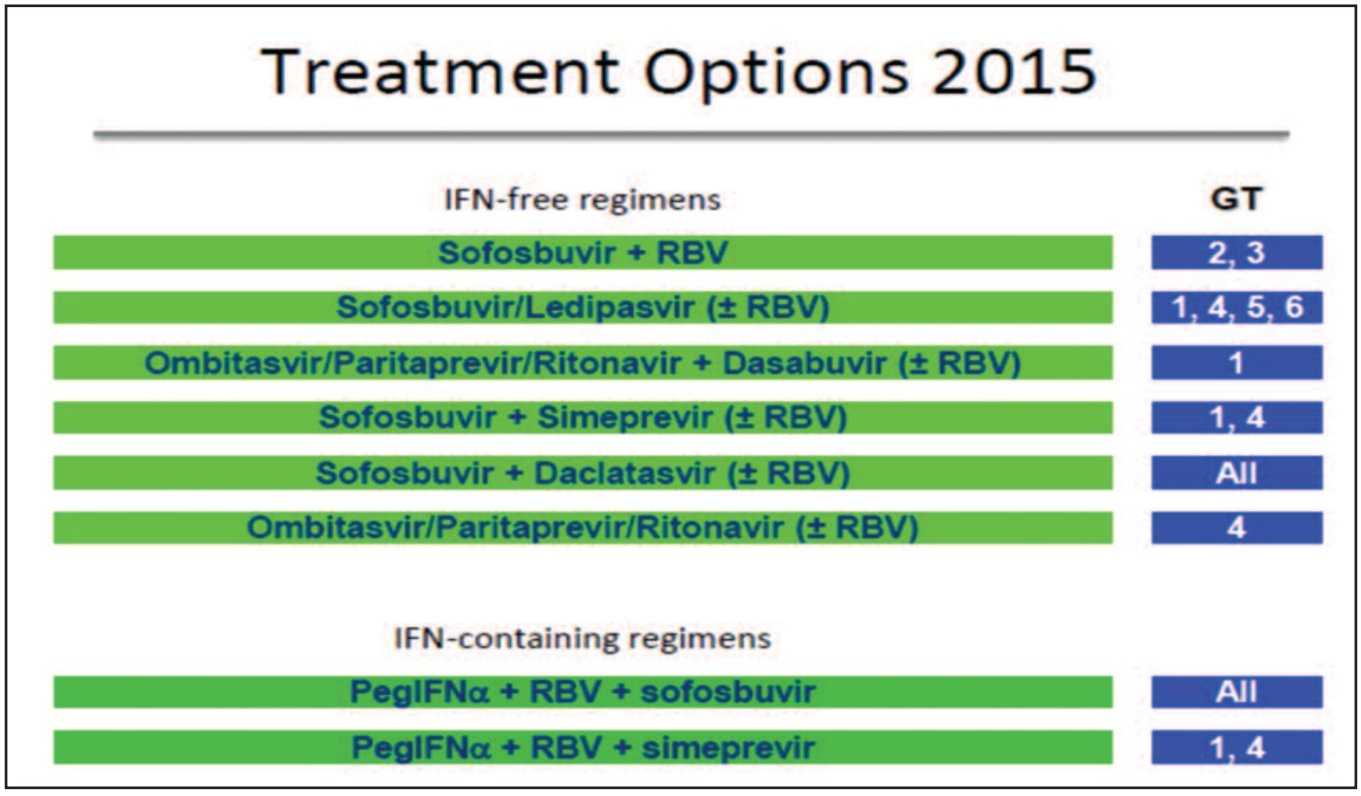
Furthermore, the real reason for treating patients with Hepatitis C early is the additional quantity and quality of life it gives people with Hepatitis C by avoiding all the stages discussed in the presentation. The number of liver complications significantly reduces and overall survival is increased, as a result of clearing Hepatitis C, also known as achieving an SVR. He also referred to a paper that reviewed articles about people with Hepatitis C and health-related quality of life, which showed an improvement in people's quality of life after achieving an SVR.

With the new era of Hepatitis C treatments, it is now becoming possible to treat all patients with Hepatitis C. Professor Geoffrey Duskeiko, from the Royal Free Hospital in London spoke about this new era and the treatments available in 2015 and beyond. There are eight treatment options available under the EASL guidelines, which are used in different degrees in different genotypes.

Professor Geoffrey Duskeiko, Royal Free Hospital.

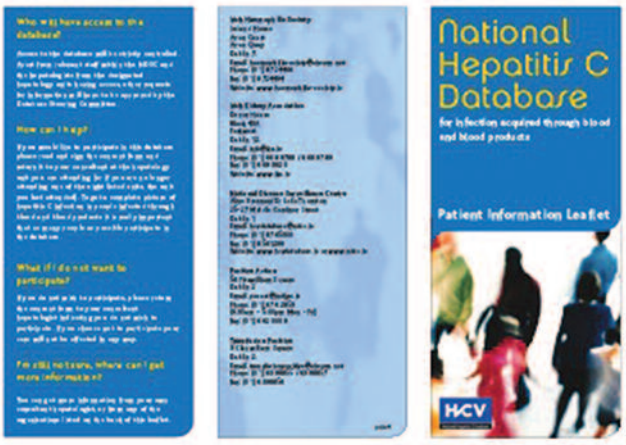
He gave an excellent overview of the current state of the art treatments. In general, patients who have no cirrhosis with genotype 1b are achieving SVR rates between 95-100%. The discussion points for this group is the duration of treatment (12 weeks or potentially 8 weeks) and if there is a need to add Ribavirin to these drug combinations.

The next group are the cirrhotic patients who have Childs-Pugh A categories with genotype 1a or harder to treat 1b's. These patients are achieving SVR rates in the 90-95% range. Again questions about the duration, this time it is 12 or 24 weeks duration. Also is Ribavirin more beneficial in this cohort? There are some further issues around the use of the drug group NS5A inhibitors, as there may be more resistance with this category of drugs. The next cohort is those with cirrhosis who are in the Childs-Pugh B and C categories. This group are achieving SVR rates of 85-90%. There are more discussions on this particular group. Duration is not as much of an issue as most patients seem to require 24 weeks of treatment. Thoughts on the use of Ribavirin switches from the additional potential benefit to the balance of the risk between the benefit and the side effects it can cause when the liver is so badly damaged. Also, if patients are particularly difficult to treat then the potential of using 3 DAA's together to stop the virus at all three sites is a potential option. The last group, achieving less than 85% success rates, are those with genotype 3 and those in the Childs-Pugh C categories and some previously treated patients. The simplest answer is to treat these patients as early as possible to prevent progression. The addition of a third DAA may also help this category. He discussed the various regimens and potentials for drug-drug interactions that some of the new drugs have



with immunosuppressant medications, cardiac medications, HIV medications and potential issues for those with renal problems in the way the current drugs are excreted from the body. It was a very comprehensive presentation and delegates got a lot from this session and the questions at the end of the session.

In the afternoon, countries had the opportunity to present their own experiences on the current situation in their country and the level of access to treatment. The UK, Scotland, Denmark, Germany, France, Switzerland, Serbia, Poland, Canada, Ireland, Portugal and the Netherlands all presented on access to treatments. Some countries have no access currently and are still using Interferon based treatments for all patients. Most of the countries had some access to the newer treatments. The priority patients in almost all countries were those with late-stage cirrhosis. Treatment was then rolled out to patients with cirrhosis, then those with F3 fibrosis with accelerating factors, such as co-infection with HIV or Hepatitis B, liver transplant patients and other medical problems. The three countries with some interesting, innovative treating protocols were Scotland, Portugal and Canada. In Canada, patients with haemophilia are entitled to treatment irrelevant of their liver damage stages, as it is provided for under the Hepatitis C Compensation Scheme that was put in place for people with haemophilia. In Scotland, a policy over the last 5 years of making Hepatitis C a national health priority is paying off with some regions of Scotland, running out of patients to treat under current criteria and they now need to move on to those with little or no fibrosis. It is still difficult, but access is becoming easier. The most interesting case study presented was the Portuguese system where a national system has been set up and over 1,000 patients have been treated since the start of the year. All patients' data are going into a national registry to improve the treatment responses and optimise the system. This has all been coordinated in conjunction with deals from the pharmaceutical companies where the price per patient reduces over time. It is these sorts of nationally coordinated efforts with long-term plans and goals, similar to what we are seeing in Scotland, which will make real steps towards Hepatitis C eradication.



On Sunday, there was a presentation and discussion on advocacy efforts from Ireland and Poland. There was also a presentation from Dr. Lelia Thornton from the National Hepatitis C Database, on the latest update for those patients who were infected by the Irish state.

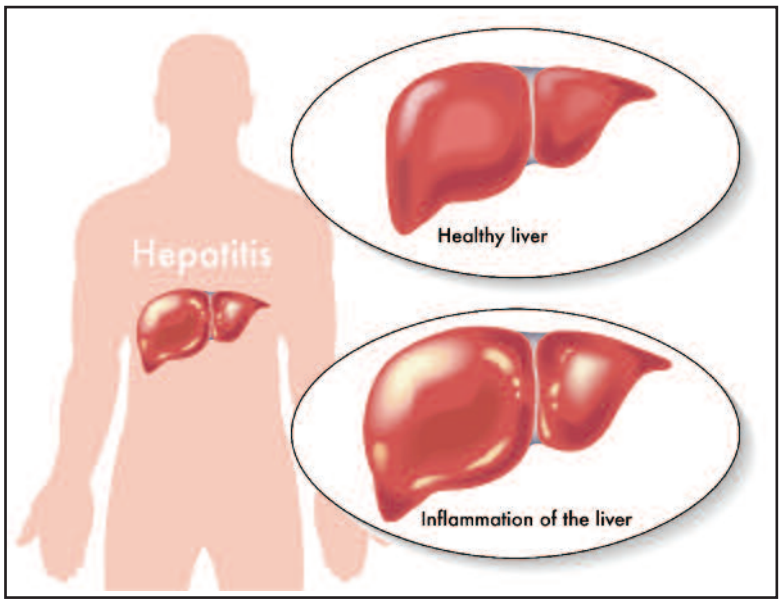
Dr. Lelia Thornton, National Hepatitis C Database.

This showed that those infected through blood transfusion or clotting factors were more likely to have died from liver-related causes than other groups. Also, almost 40% of those with bleeding disorders were showing signs of serious liver disease and had the highest rate of liver cancer (7.1%) of the population.

The final session of the weekend was on optimising support for members of haemophilia organisations. In many cases, haemophilia organisations are working to get access for their members on the new treatments. This session focused on supporting people with haemophilia in preparing for treatment, discussing the importance of awareness of potential side effects and putting past treatment experiences in perspective when considering new treatments. The session also looked at the importance of maintaining contact with members after they have achieved SVR's, especially if they still have cirrhosis. Patients who are currently waiting for transplants was also discussed, those for whom treatments have failed and how we can provide support to them.

The conference was informative. There were good conversations and discussions over the course of the weekend which emphasised the importance of access to the new treatments, as well as giving an excellent opportunity for delegates to share knowledge and ideas on how to advocate for access to the newest treatments.

LIVER TRANSPLANT MIGHT BE MY NEXT STEP – WHAT HAPPENS NEXT?



With the speed of development of new treatments to cure Hepatitis C over the last few years, many articles, when written, are out of date before they are even published. Fortunately, this article will be useful for a while longer, but hopefully in the near future, it should be resigned to the history books and referred to only in the context: "*Do you remember when Hepatitis C patients needed a transplant?*"

Liver transplant is an all too common consequence of Hepatitis C. With Hepatitis C, if cirrhosis gets to the point where the liver can no longer carry out all the functions that is required of it, then a liver transplant needs to be considered. At this stage being referred and/or assessed for a liver transplant can be a daunting experience. There are a number of considerations that are taken into account in this process. Hopefully, this article will shed a little light on this path.

Referral

St. Vincent's Hospital in Dublin is the centre for liver transplantation, so if you are attending this hospital as your primary hepatology centre, no referral is required. If you are attending another hepatology centre and are being considered for a transplant, you will be referred to St. Vincent's for assessment. It is important to acknowledge, one of the most difficult aspects about this part of a potential liver transplant process can sometimes be the wait. I do not mean the referral itself as this happens relatively quickly. The wait I am talking about is, as someone with end-stage liver disease, when you can feel quite sick, it can be some time before you are unwell enough to require a referral. In an ideal world, with no limits on availability of livers for transplant and with a survival rate of 100%, people would get a liver transplant straight away, but unfortunately we don't live in an ideal world. So the management of symptoms and monitoring can be the best option during this stage. This can be frustrating and hanging around in "limbo", waiting to be referred, can be difficult. It may be useful to talk to others in a similar situation, or a professional if you are in this position. Keeping appointments is also important at this stage for two reasons: firstly, attending appointments means your current situation is being monitored, so any problems such as ascites, varices, encephalopathy, etc. can be managed and secondly, if things change more rapidly, then a referral happens quickly.

Patient Selection

When is a decision made when it comes to being assessed to go on the transplant list? A decision is made based on survival benefit and what is best for you. In the first year after transplant, mortality is about 1 in 10 people (10%) and 1 in 5 people (20%) in the first five years. In this situation if your own liver has a better than 90% chance that it will be functioning in a year's time and will be still keeping you alive, or a better than 80% chance that it will be functioning in 5 years' time, a person will not be considered for transplant at this stage. This may be hard to hear but makes sense. If your own liver gives you a better chance of surviving than a new one, then there is no need to be listed at that stage. It is when the chances that a new liver will give you a better chance of surviving, that a patient will be assessed for the list. Your hepatologist will refer you to St. Vincent's ahead of

time. On some occasions, when a referral happens, it still may be too early for an assessment for listing on the liver transplant list based on the above risk. At this stage, you will be continued to be monitored by your current hepatologist, and St. Vincent's, for changes.

When the situation starts to tip towards a liver transplant being the best option and being considered for listing, a number of things are discussed with you at this stage. Firstly, what is the level of cirrhosis that is in the liver? They assess this using three scales; the Childs-Pugh (CPT) Score, the MELD score and the UKELD score. These methods are based on a combination of blood test results and other events such as ascites and encephalopathy. Generally speaking, patients with a CPT rating of B or C, a MELD score of 15 or higher and a UKELD score of 49 or higher, will be considered for listing on the transplant waiting list, as this is closer to when the odds of a liver transplant being more successful than your current liver start to balance out.

Liver Cancer (HCC) is another aspect that is considered when putting people on the list or if people are already on the liver transplant list. Some patients with Hepatitis C develop liver cancer, when they have cirrhosis. This can have a negative effect on the outcome of a liver transplant, and criteria has been developed to give people the best chance of survival. This criteria (known as the Milan criteria) states that if a person has one liver tumour greater than 5cm, or three liver tumours greater than 3cm in size, then a transplant is not recommended. This again goes back to survival benefit for the person as well as the best use of a donated organ. There are, however, methods to slow down the progression of liver cancer, to maximise a person's chance of getting onto and staying on the liver transplant list. Radio Frequency Ablation (RFA) or Trans-Arterial Chemo Embolization (TACE) kill the cancer cells and prevents the tumours from growing. This is very successful and can give many people the time they need to wait for a liver transplant.

There are also other contra-indications for not getting on the list. If there are other medical issues such as severe heart or lung problems or other types of cancer, where the survival benefit of a new liver has little impact on the overall survival of the person, then they are not put on the transplant list.

Other aspects for not listing patients are continued substance abuse, either drugs or alcohol, but in general if an individual has shown that they can abstain for a significant period of time, then the assessment will continue. Other aspects like compliance and in rare situations, social supports also play a part in patient selection. If a person is very unstable, or missed a lot of hospital appointments, or contact is minimal, or adherence to current medications is not good, then they are less likely to be selected for assessment.

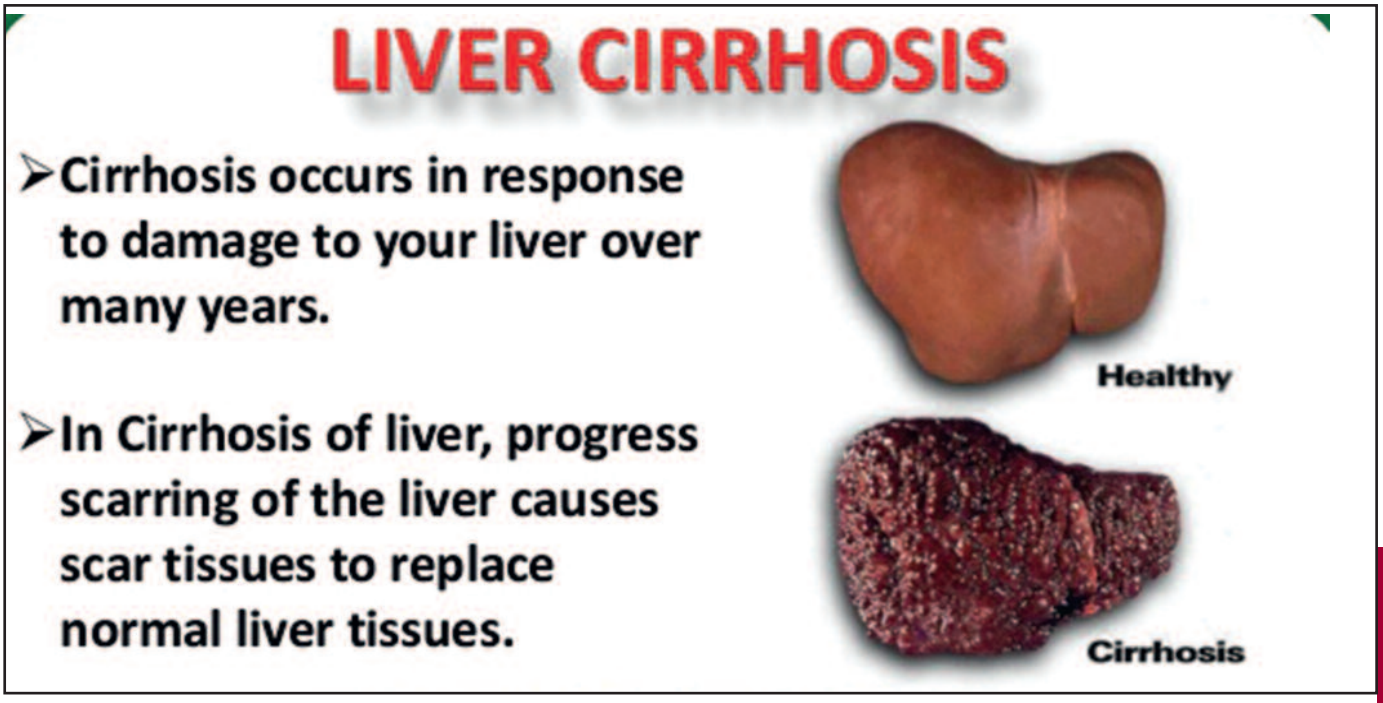
In all of the above, clinicians will give every opportunity, to anyone who is in this situation to be considered to go onto the liver transplant list. However, the need for liver transplants is high and availability of donor's livers is low, so in order to give the best chance to the person needing the liver transplant, as well as respecting the memory of those who have donated their organs, the criteria is strict.

The final hurdle

Once a person is selected for assessment, a set of tests are carried out over a six-week period in St. Vincent's. This may seem long, but it is the most effective way to get all those who need to be assessed each year. The six weeks are organised by the Liver Transplant Coordinators. The assessment looks at every aspect that might cause a problem while on the list, or in surgery, or post-surgery. There are no stones left unturned and nothing is left to chance. During the six-week period, the heart, lungs, blood, kidneys and teeth are all assessed in depth. The heart rate is checked at resting speed and also at stressed scenarios, either using a treadmill or stationary bike to stress the heart. Alternatively, a stress echo can be done if the person cannot use these, where they inject a drug that increases your heart rate. Based on these results, they will refer you to the cardiac unit to ensure that during surgery and, post-transplant, your heart is in full working order. The cardiac unit may look at the requirement for an angiogram, or stenting, or bypass surgery, if it is needed.

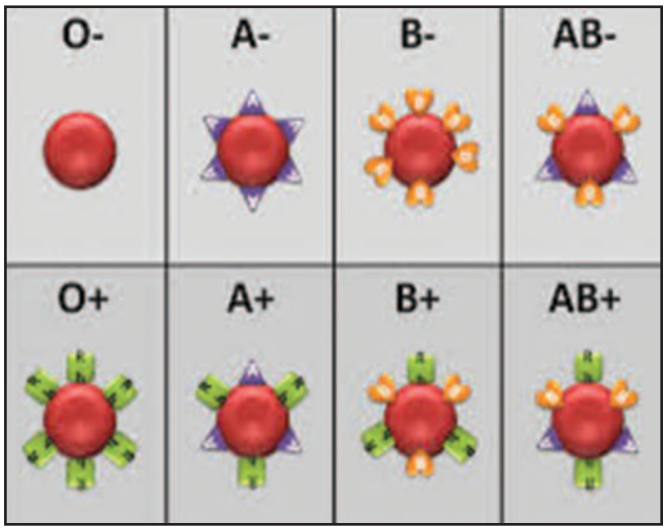
The next step is to check the lungs; how strong they are, how they take in and release air and if there are any infections. A full set of liver bloods are carried out as well as kidney bloods and a check for other viruses. The teeth and gums are checked to make sure there are no bacteria hiding in gum disease, or back teeth that might result in an infection at a later stage. The whole process is very comprehensive. In the event that anything shows up during the assessment, this will be dealt with well in advance of the patient being listed. This is to make sure that once you are listed, everything possible has been done to reduce the risk of you coming off the list for any reason.

After all of the assessments are carried out, the person then meets with the surgeons and anaesthetists for their assessment for surgery. Finally, it comes down to a multidisciplinary meeting, looking over every aspect of the results of the assessment and the individual's situation. The decision is then made by three physicians and three surgeons. A majority of four is needed in order to be listed for liver transplant. Again these decisions are not taken lightly, and every opportunity is given to those patients who are being assessed.



The Liver Transplant

If a patient is put on the list, they are listed according to their blood types, as this offers the best chance of the liver being accepted. So a donor liver with blood type O will go to a person on the list with blood type O. The same goes for A, B and AB.



At this point, the waiting begins again. It would be hoped that anyone on the waiting list would get a transplant within a year or two, but the period of time is difficult to guess, and there is wide variation. Some people get sicker faster and move up the list. Furthermore, there are four separate lists (A, B, AB, O) all with different lengths, as they only match the blood type of the donor to the blood type of person receiving the transplant. Blood type O is the most common, followed by A and B and then AB. This means the chance that the next available liver is of O blood type is higher. However, this is a larger list so the time can be longer. On the other hand the AB blood type list is shorter, but as an AB blood type is less common, the number of new livers becoming available is a little less, so the time on the list can be some time. It is very hard to predict how it will go, and again this can be a difficult time because there is a plan put in place, but waiting to put it into action can be frustrating. In between being put on the list and getting a new liver, you will also see a dietician who will work with you to get you as fit as possible for the surgery and recovery.

When a liver becomes available and is matched to your blood type, and you are next on the list, a call will be made to you on your mobile. This call can come at any time, so if your phone is on its last legs, it is strongly advised to have one that has a good battery life, and you carry a charger with you. Some people in the past have even carried extra batteries if they were leaving home for a long time. Most people who are on the list generally don't feel up to big holiday trips outside the country, but if you need to leave the country for a wedding or funeral, or for an emergency, you need to let St. Vincent's know. You will be taken off the list for that time as you will not be able to get to the hospital within enough time if a liver were to become available.

When a liver becomes available, and you receive the phone call, you make your way to St. Vincent's as quickly as possible. As you make your way to the hospital, the donor's liver is being assessed for its size, how healthy it is and is there much fat around it, etc. It might be found that the liver is not a viable option. The reason they call you as this assessment is going on is so that the time between finding out about the liver and performing the transplant is a small as possible and that the liver is in

the best condition it can be in when it is transplanted. It may be the case on your way to the hospital, or in the hospital, you might be told it is not a good possibility, and the transplant will not go ahead. Most people get a new liver on their first call. However, some may take a second or third call before a liver is found that is viable. Once you are in the hospital, you will be prepped, which could take two to three hours on the ward, checking ECG's, X-rays, etc., before you go in for the surgery. The liver transplant operation itself can take between 6-8 hours overall.

Post-Transplant

People are expected to be in hospital for 3-4 weeks of recovery, to check that the liver, heart, lungs, and everything else, is stable. They will also look at how the immunosuppressant drugs that need to be taken, to try to prevent the body attacking the new liver, work. Depending on the person, and how they respond, this can take some tweaking. Many people recover quickly. Some can be out before three weeks, and some people have complications and could be in longer. This is hard to predict, but all the work put in beforehand, with the assessment and the nutrition, will improve the chances of getting out quicker.

After being released from hospital, for the first four to six weeks, it will be weekly visits to the hospital to keep an eye on things and to make sure that all the blood results are where they should be. If there is anything a little higher or lower than it should be, which can be common after transplant, the hospital will monitor it and will assess the immunosuppressant drugs continuously, to make sure they are doing exactly what they are supposed to. They will also check to see if there are any side effects. After this, the appointments will start to be moved out to longer time periods, one after two weeks, then a further four weeks and then every three months. At any stage when you are at home, you should notify the hospital if you have any fever, vomiting, diarrhoea, redness or increased pain around the scar after the operation. The sooner you inform the hospital, the quicker it can be dealt with.

Hepatitis C - Treat Before or After a Liver Transplant?

During the time from discussing being referred for transplant assessment, to the weeks or months following the liver transplant, there will be conversations between you and your hepatologist about treatment for Hepatitis C. This is an interesting discussion and is evolving all the time with more experience and knowledge of the new treatments. There are a number of options that your team will be looking at.

Option 1: Treat before the transplant and remove Hepatitis C from the situation altogether and not put the new liver at any additional risk. Considerations for this option are; the new treatments are not as toxic as Interferon based treatments, so a person with even the most damaged liver can undergo these treatments. If they clear it, it could give them more time to wait for a new liver if one is needed. The problem however is that with a liver that is so badly damaged the blood circulation is not very good so the drugs may not get to every piece of virus and, as a result, the success rate in clearing the virus is reduced.

There is another aspect to consider. If the liver is so badly damaged and a person is on the waiting list will that person be able to get through the full course of treatment before they get a new liver? Some studies suggest that if treatment is taken for at least 30 days before a liver transplant, then there is a very good chance Hepatitis C will not come back after the transplant. However, if you have a liver transplant before this time, Hepatitis C may return, and potentially develop resistance to one of the drugs, reducing the possibility of success after transplant.

In one discussion recently there was a suggestion of using the MELD scores to help with the decision. People with a MELD score of less than 20 might be better treated before the transplant. A person with a MELD of greater than 30 might be better to be treated after transplant. Those in the 20-30 region is a grey area and a lot of unknown answers at the moment.

There are pro's and con's to treating an individual before and after a liver transplant, and there are no hard and fast rules. It is a quickly evolving situation and in a few months there will be even more information available. These discussions and considerations, and balancing of risks are going on constantly in the clinicians heads. Every decision will be based on your circumstances and what is the best option for you.

If you are waiting for a referral or are on the waiting list, we hope your wait is short and the best of luck with your new transplant. This can be a long, sometimes frustrating, and sometimes a tough road, but the benefits at the end are worth every step.

Option 2: Treat after the liver transplant. If you have not cleared Hepatitis C, the new liver will be re-infected with Hepatitis C again. The new treatments are much easier on the liver as the side effects are significantly reduced and with a new liver, without cirrhosis, the chance of getting rid of the virus might be higher. With the rollout of treatments in Ireland, people who are post-transplant will soon be able to get access to the new treatments and will be able to start as soon as they are stable enough to take them. However, treatment post-transplant has some other issues. In some cases, this reinfection can be rapid and cause further complications.

ACCESS VERSUS COST

Along with the excitement from the medical profession, and the relief of patients, comes enormous controversy over the new treatments and a health systems ability to pay for them. This is not a conversation that anyone wants to have but in reality this is the limiting factor in the scale of treatment. Hepatitis C affects approximately 130 to 150 million people globally. There are approximately 12,000 people in Ireland identified, but the overall number of people infected could be between 20,000- 50,000. Every year, at least 700,000 people die from complications due to Hepatitis C although with the new treatments these can be easily cured.

Treatment with Interferon and Ribavirin today costs approximately €10,000 - €20,000. However, as we know the main drawbacks to treatment using Interferon and Ribavirin are the side effects, the lengthy duration and the limited success rate. Many people find it difficult to get through Hepatitis C treatment for six to twelve months because of the side effects. The most common side effects are anaemia, fatigue, headaches, nausea, depression, insomnia, and hair loss. There is also a wide variety of success rates with different genotypes from 40-90%. The latest DAA treatments significantly shorten the duration of treatment, with milder side effects, and have success rates in 90% or more.

In comparison to Interferon and Ribavirin treatments, (in the US where prices are listed publically) a twelve week course of Sovaldi, in 2014, had an original listed price of $84,000 and Olysio is listed at $66,000. Later in the year two other treatments, that were combinations of drugs came on the market. Harvoni had a listed price of $94,500 and Viekira Pak was listed at $83,300. In France, the 2014 price of Sovaldi was quoted at €60,000 and in the UK the course of 12 weeks cost £35,000.

The biggest issue is not the cost-effectiveness of these treatments but the budget impact on national health systems that these treatments create. In many countries, due to price, there has been a very slow tiered release of these treatments. This means that patients in the most need will get access to these first. For example, patients who have decompensated cirrhosis, or on a liver transplant list, or those with cirrhosis and/or accelerating factors. This is only a tiny portion of the overall Hepatitis C population. So what is being done about this?

Firstly, and most importantly for those patients listed above, the release of these drugs is life-saving. Patients need these medications, and in many countries, even at the original prices, many of these drugs are cost-effective. In the near future, many of these patients will avoid hospitalisations, liver transplant and other healthcare resources which would cost significantly more.

Secondly, once Harvoni and Viekira Pak (called Viekirax/Exviera in Europe) became available in the US and Europe, as well as Europe having the additional drug of Daklinza available, reports of significant price reductions in the current market began appearing. In early 2015, one company stated that the average discount in the US for these drugs is expected to reach 46% of the original price this year, with discounts for public payers to be more than 50%. This is expected to be on the back of medical insurance companies and pharmacy chains signing deals under “preferred drugs schemes”. In France and Germany, a reduction to €41,000 was announced on Sovaldi and price negotiations are on-going in many other European countries. This is only the start of further downward pressure on costs from payers, patients and competition for the market.

Furthermore, there have been interesting suggestions on the pricing of these medications, with risk sharing between the companies and the payers. The first option suggested is a simple ‘pay per course of treatment’ option. The aim is to have an effective regimen at the lowest price. This will effectively be a “preferred drug scheme” for a specific genotype, which has been mentioned above and is expected to be in many countries in the near future. Another suggested pricing scheme is ‘cost per patient’. A patient receives 12 weeks of treatment and if they are clear at week 12 and relapse, they get an additional re-treatment for 24 weeks free of charge or if the patient is not clear at week 12, they continue for an additional 12 weeks free of charge. So the payer only pays for the first 12 weeks of treatment in either case. The last suggestion is a ‘pay per cure’ model. This is similar to the ‘pay per patient’ in how it is rolled out, but the main difference is that if the patient is not SVR negative (cured) 12 weeks after treatment and has proven to have taken the medication appropriately, then no payment is paid for that patient. This is the ultimate in risk sharing, but is easily achievable at current prices, particularly when research from Liverpool University shows that the 12-week course can be mass-produced for just US$101!

This brings me to my final point. In 2014, the Hepatitis C market for the new Direct Acting Antiviral's was in excess of $10 billion. The main issue (as is with almost all health care systems) is that drugs are not associated with the cost of developing these new drugs, but with the cost compared to previous treatments in the system. It is therefore my belief that it will be a struggle for all new innovative drugs coming to the market, to make a significant impact on patients' lives, without the realignment of what the costs are, and what the return for developing new drugs should be.