Positive News

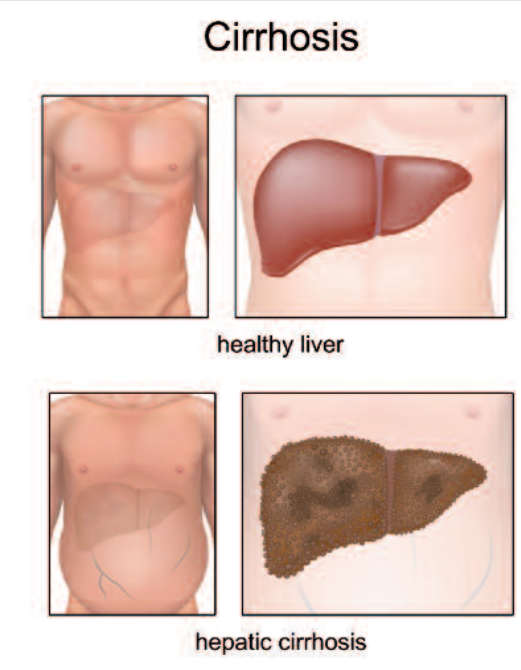
Information Magazine for people with Hepatitis C and HIV

The Irish Haemophilia Society

Representing people in Ireland with haemophilia and related bleeding disorders.

Hepatitis C - Treatment in people with haemophilia, the results to date

From July 2012 to October 2013, a total of fifteen persons with haemophilia or related bleeding disorder with Genotype 1 Hepatitis C had commenced triple therapy treatment consisting of Pegylated Interferon, Ribavirin and a Proteate Inhibitor (either Incivo or Victrelis). The Irish Haemophilia Society has provided, and continues to provide, support, encouragement, assistance and information to all our members on treatment. To date, a total of seven people with haemophilia have completed the course of treatment with two individuals requiring a twenty four week course of treatment and five individuals requiring a forty eight week course. All seven individuals were negative for the Hepatitis C virus at the end of their treatment (an end of treatment tesponse - EOTR). Of these seven individuals, three are now at six months post completion of treatment, and all 3 have achieved a sustained virological response (SVR) which, effectively, is a cure. A further four individuals are continuing their treatment. The treatment failed for three individuals with their treatment being stopped and unfortunately, a fourth individual died while on treatment. We will continue to monitor and report the outcome of treatment in the haemophilia group.



Support from the Irish Haemophilia Society

If you are on treatment, and there is something that the Society can help you with, please do not hesitate to contact the office on 01 6579900.

We are committed to offering practical support and assistance to members on Hepatitis C treatment.

Some of the supports available to members are:

- Accommodation Facility
- Financial Assitance
- Personal Support

Please contact Anne Duffy on 087 232 0255 if you have any concerns or queries in relation to treatment. We are here to give as much support as possible, during your course of treatment.

Edition: December 2013

Getting through treatment – the Irish experience

In 2011, two new treatments for Hepatitis C genotype 1, were licensed. These were Boceprevir (Victrelis) and Telaprevir (Incivo), used in combination with Interferon and Ribavirin. In late 2011, the first Irish person with haemophilia started these treatments and by March 2013, eleven people had started or finished treatment. Studies have shown that approximately 20% of people stopped treatment early as a result of the side effects of these drugs. However, within the Irish group of people with haemophilia on Hepatitis C treatment, nobody stopped treatment early as a result of side effects. The Irish Haemophilia Society (I.H.S.) asked these members what they had done to prepare for treatment, what their expectations of treatment were and how those changed during treatment. These members filled out a questionnaire in March this year and were asked to take part in a discussion group in April which was guided by the results of the questionnaires. A number of these people with haemophilia, and their partners took part. The questionnaire looked at preparation for side effects, preparation for impact on daily life including work, daily activities and the subsequent reality of treatment.

Some of the early results show that the biggest factor in the decision to start treatment was due to the availability of new treatments. Discussions with the hepatology nurses and clinicians about their current clinical position had a large impact. The person's age had the least effect on the decision. The biggest source of information that people used to get a grasp of the road ahead was the information meetings organised by the I.H.S. This was followed by information by the hepatology clinicians and nurses. At I.H.S. meetings, those who spoke were mainly clinicians and the nurses who would be caring for people when on treatment. Attending these meetings allowed most people to get answers to questions that they hadn't even thought about in relation to treatment, side effects and coping. The least frequent information source used was pharmaceutical industry leaflets.

In preparation for the side effects, some people informed specific family members and friends that they were starting treatment. They prepared themselves mentally for treatment. In relation to the treatment itself, as skin rashes were assumed to be a major potential side effect, through discussion with the hepatology nurses and people who had done treatment, people moisturised or washed their skin with non-perfumed creams (e.g. Silcock's Base or E45). Some prepared a list of medications that could assist with side effects before they became a major problem. People did things that saved effort or trouble later such as, arranged home help, prepared frozen meals, or fixed minor problems around the house. Specifically for Telaprevir (Incivo), people prepared for the diet of 20g of fat with each tablet. They did this by figuring out what was 20g of fat in certain foods, and having alternatives for the times when they did not want a specific food type.

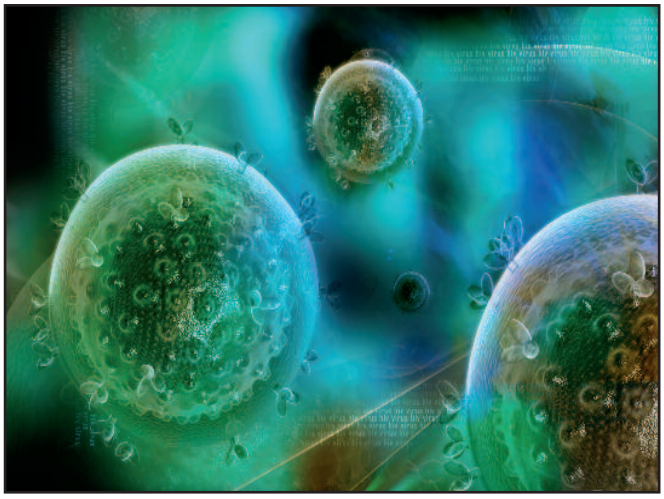
From a work point of view, most were either not working or reduced their work load. For those who were working they reduced their work load significantly by between 25-50%. In relation to Telaprevir (Incivo), reducing work load was more in the first 12 weeks and less for the remaining time. With Boceprevir, it required as less of a reduction for most of the length of treatment. 72% of respondents rated the impact of the triple therapy treatments as severe to very severe and the same number said that side effects were more severe or much more severe than had been anticipated. The pegInteferon and Riabvirin had relatively well characterised side effects, which are flu-like symptoms, depression, fatigue, reduced concentration, mood swings, coughing, breathlessness and sleep disruption that appeared with varying degrees in different people. Adding in a third drug tendered to add or magnify these side effects.

With Boceprevir, a constant metallic taste in their mouth was described, and some people used plastic cutlery to reduce the problems from this side effect. Anal discomfort or itching was described in association with Telaprevir. However, this may have been due to individuals not taking the full 20g of fat with the tablets. Some felt that increasing the amount to 21-22g helped. Skin rashes were not as common as expected, but itching and skin irritation were. Common places for these were where there seemed to be the least amount of muscle or fat, i.e ankle, hands, fingers, ears, etc. This was generally dealt with by moisturising and/or medications prescribed by the hepatology team. The most significant side-effect of Boceprevir and Telaprevir was a raised rate of anaemia (lack of red cells, and therefore oxygen, in the blood), which led to one of the main side effects which was fatigue. One of the individuals said "although you are told about the side effects, I don't think anyone can really tell you how sick you can feel on a bad day". However in further discussions the same individual said "the side effects have been tolerable but there have been some hard weeks." This message really gets to the heart of the matter. Obviously there is no point in saying that these treatments are easy. Some days can be very difficult but there is an end and a very good reason you are doing this, which is the focus and the drive for a lot of people.

This also leads on to the importance of support. When these individuals were asked about what were the major supports during this time the three top responses were firstly your partner/spouse/family members, secondly the support of the staff in hepatology and thirdly meeting with other people who were on treatment. As stated already these are the early results of how the individuals themselves coped on treatment. In a future issues of 'Positive News' we will be discussing these in more detail as well as the ideas and thoughts of the partners who also had to go through the treatment, just in a different way.

The future is speeding towards us, and it looks promising

You know that feeling when you have waiting hours for the bus to come and then two come along together. Well that is what it has been like in Hepatitis C treatment for the last ten years. The only difference really is that after those two there is an entire fleet that may be coming behind them. It really is a fascinating time in Hepatitis C treatment. A little tip, to get the most out of this article you should know, your genotype, IL28B combination, how you responded to treatment last time and your fibrosis stage (see the reminders section).



Current Treatments

At present, the regimen for treating Hepatitis C consists of two or three drugs in combination depending on the genotype, each with their own side-effects.

Genotypes - 2, 3, 4, 5, 6

A combination of pegylated interferon and ribavirin (pIFN/RBV) is still the only treatment available for these genotypes at the moment. The main reason is the focus has been on Genotype 1 as it is the most common. The SVR rates in Genotype 2 and 3 are around 80% with the pIFN/RBV. The Pegylated Interferon (pIFN) is a sub-cutaneous injection once a week and the Ribavirin (RBV) is taken in tablet form twice a day. The treatment currently lasts for either 24 weeks or 48 weeks.

Reminders / Glossary of Terms

SVR *- stands for 'sustained virological response' and means there is no Hepatitis C virus evident in the blood 24 weeks after treatment has ended, currently the accepted definition of a cure. Subsequent relapses are very rare. If there is no virus evident twelve weeks after treatment has ended, in over 99% of cases this is still the case after 24 weeks. It is sometimes written with a number after it. The number stands for the number of weeks after the treatment is finished. Example: SVR4 is 4 weeks after the end of treatment.*

Genotype *(G1a, 1b, 2, 3, 4 etc.) - Hepatitis C comes in many different genotypes (varieties), with very different rates on how effective treatment is. In general, G1 and G4 (especially G1a) are the hardest to treat – though now with new drugs G1b in particular is more treatable. G3 is next hardest to treat and G2 the easiest to treat.*

IL-28B *– Is a protein in the body that plays a role in the defence against viruses. There is one point on this protein where there are 3 possible combinations. These are CC, CT and TT. Individuals with the CC configuration have the best response to treatment followed by those with CT and those with TT have the worst response.*

Naïve *– Never tried treatment before.*

Null Responder *– Is someone who has tried treatment before but it had little or no effect on the viral load and the viral load was never undetectable during their treatment.*

Relapsing Responder *– Is someone who has tried treatment before, the virus was undetectable at the end of treatment but it came back in the six months between finishing and week 24 (SVR24). So, they do not achieve an SVR and this person is referred to as a relapsing responder.*

Fibrosis *- Scarring to the liver (but the liver is still largely able to do its job). There are various grades of fibrosis.*

Cirrhosis *- Large portions of the liver are replaced with scar tissue; blood flow through the liver is restricted and the person will probably be suffering from symptoms caused by poor liver function.*

pIFN *– stands for the drug pegylated (longer lasting) Interfereon. Injection once a week.*

RBV *– Stands for the drug Ribavirin. Tablets twice a day.*

pIFN/RBV *– Stands for both together.*

Genotype 1

Genotype 1 has two sub genotypes, G1a and G1b. The previous treatment was the same as with all other Genotypes: Pegylated Interferon and Ribavirin (pIFN/RBV). The SVR rates however were much less at 40-50% for people with Hepatitis C alone and about 30-40% for people who are co-infected with HIV and Hepatitis C. In 2011, two new drugs were licenced to tackle this more difficult Genotype. These were known as G1 specific protease inhibitors. These are tablets taken in conjunction with the pIFN/RBV. These are called Telaprevir (Incivo) and Boceprevir (Victrelis). We have discussed these in detail in previous "Positive News" newsletters, so please check out our website or contact us for more information. For the first time, people with G1 have achieved 67% to 75% SVR rates in studies. However, the likelihood of SVR depends on someone's individual situation. People who already have cirrhosis respond to treatment less often than people in earlier stages of liver disease. If previous treatment had little or no effect (null responders), the prospects are not as good if the same medications are taken again with the addition of the extra drug. In studies to date, null responders with cirrhosis who took the Telaprevir triple therapy only had 14% response rates. On the other hand, Relapsers with Genotype 1 have good prospects. In pre-licencing approval studies with Boceprevir and Telaprevir, 75 to 88% of relapsers achieved an SVR.

Note: Telaprevir

Until now Telaprevir tablets have had to be taken three times a day and at eight-hour intervals, in order to avoid the virus from becoming resistant to the drugs. Telaprevir must also be taken with 20g of fat. This is not easy for many people as Hepatitis C treatment can cause nausea and loss of appetite. A new study has shown that Telaprevir can be taken twice a day, resulting in the same SVR rates. Side-effects were similar in groups on twice a day and three times a day, regardless of whether people had cirrhosis or not. However, anaemia occurred slightly more often in the twice-daily dose. This appears to be good news as it may turn a regimen that is difficult into a more manageable one.

HIV / HCV Co-Infection

People who are co-infected with HIV and Hepatitis C have a greater risk of developing late-stage liver disease such as cirrhosis and liver cancer. Previous treatments with pIFN/RBV were less successful for people in this situation. A new study now reveals that triple therapy with Telaprevir, pIFN/RBV has similar SVR rates in those with HIV co-infection as in people with hepatitis C alone. In 74% of previously untreated people, Hepatitis C was eliminated using triple therapy, whereas only 45% of trial subjects achieved this using dual therapy. A second study by the same team has found a 62.5% SVR12 response rate with Boceprevir. The new drugs are mostly being used in people who have hepatitis C only (mono-infection), however there are a few clinical trials in co-infection. As there can be many interactions with HIV drugs, it is important that this treatment is monitored by doctors who are experienced in treating both HIV and Hepatitis C and who can customise the range of HIV medications.

Cirrhosis

People with cirrhosis, who are already seriously ill, have less time to wait for future treatments but respond less often to current triple therapies and also have a significantly higher risk of complications. In a French study of people on Telaprevir or Boceprevier, triple therapies, 50% of people with cirrhosis had complications such as infections, and more than 4% progressed to decompensated cirrhosis. There were ten deaths. Severe complications usually occurred in people whose liver function was already significantly impaired before treatment was started. As you may expect, the more diseased the liver the greater the treatment-related risks. Without treatment, however, people with cirrhosis are at risk of dying within a few years. The decision for or against starting the current triple therapy is therefore not easy for those who have cirrhosis. Individual cases should be discussed in great detail with your doctor and treatment should be well supervised. The further advanced the cirrhosis, the more likely the possibility that a transplant will also be considered.

Side Effects

There is a drawback to the new triple therapies. There is an increased number of side-effects reported. The pIFN/RBV therapy has a generally well defined set of side effects (interferon causes flu-like illness and depression, amongst other things, and ribavirin causes anaemia). The addition of a third drug has magnified some of these side effects and added some additional ones dependant on which new drug you may be on.

With Boceprevir, a metallic taste, in particular, was observed more frequently than with dual treatment. With Telaprevir, skin rashes are more common, sometimes requiring treatment. In addition, discomfort and itching in the anal area is frequently reported. The most significant side-effect of Boceprevir and Telaprevir is probably a raised rate of anaemia (lack of red cells, and therefore oxygen, in the blood). If Boceprevir or Telaprevir are added then ribavirin-related anaemia can increase. On the upside, anaemia is a sign that treatment is working. People who experience anaemia as a side-effect achieve SVR more often than people who do not. It was reported from three American clinics that up to 21% of people taking Telaprevir stopped treatment early. This has not been case in the Irish people with haemophilia cohort so far, with no one stopping treatment as a result of side effects. You can read a description of the side effects and coping skills used by the members of the IHS in getting through treatments (see page two).

Not everyone with Genotype 1 requires three medications. One study suggests that some people, despite having Genotype 1, would have a good chance of eliminating their Hepatitis C with two medications. This group is characterised as having had no previous treatment, no cirrhosis, low viral load (<600,000 before treatment) and no viral detectability after four weeks of treatment. If all these favourable factors come together, the chances of success in the study were just as high regardless of whether the trial participants added boceprevir or not after the fourth week (90 versus 89%). This applied to around a tenth of people with Genotype 1.

What the future may hold?

Numerous new drugs are being explored. The first innovations we can expect will be more triple therapies, in which another drug with fewer side-effects is added to pIFN/RBV, while for particularly stubborn infections, quadruple therapies will be tested. It's important to remember that the new drugs don't work equally well for everyone, and in particular, some only work, or work well, with certain HCV genotypes. In the future, doctors and patients will have to consider the choice of medications very carefully. In addition, a novel version of interferon called pegylated interferon lambda is being researched. This produces fewer side-effects than pegylated interferon alfa (used in current treatment).

Direct Acting Antivirals (DAA's)

The development of direct-acting antivirals (DAAs) has been described by many as revolutionary. These are very different in the way they work compared to pIFN/RBV. Basically, the pIFN/RBV alters the ability of your own body to attack the virus. These new DAA's are different, as the name suggests, as they directly attack the virus itself to prevent it from replicating (copying itself). There are 3 main types at the moment, Protease inhibitors, Polymerase inhibitors and NS5A inhibitors. These have different mechanisms of preventing replication by preventing different sections of the virus from doing what they are supposed to do. They can generally be distinguished by the name

- HCV Protease inhibitors – ending in 'previr'
- HCV Polymerase inhibitors – ending in 'buvir'
- NS5A inhibitors – ending in 'asvir'

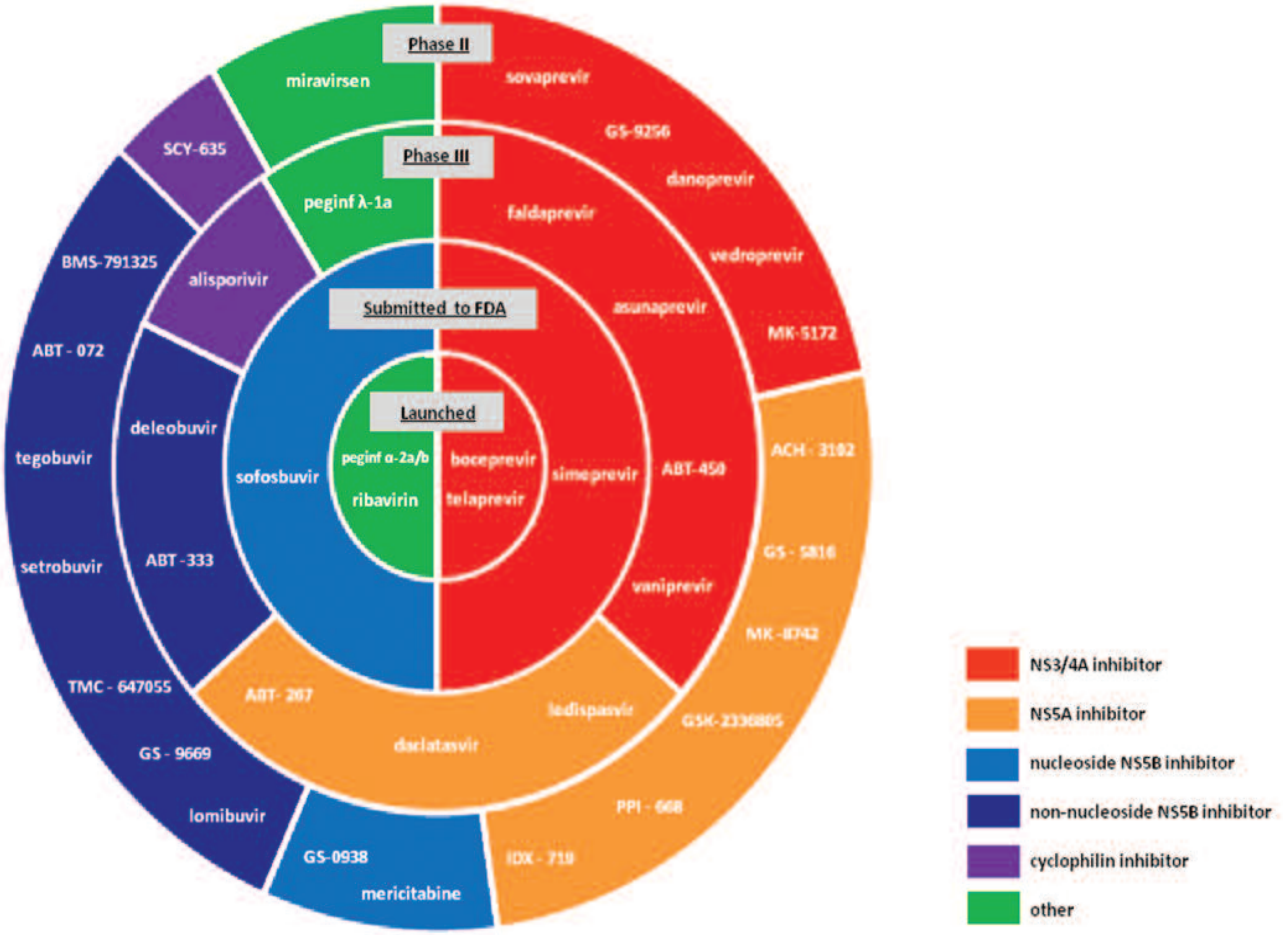
The first approved DAAs, were protease inhibitors boceprevir (Victrelis) and telaprevir (Incivo). Many of the next generation Hepatitis C drugs now in the pipeline are better tolerated, more convenient and raise SVR rates even further – often into the 90 to 100% range for people with the right predictors. As add-ons, they improve the efficacy of Interferon-based therapy, but the real revolution will be all-oral, interferon-free regimens. Table 1 below shows how the future may look, based on current studies.

		2001	2001-2011	2011-2014	Estimated 2014-2015	Estimated 2014-2016	Estimated >2016
		Unpegylated IFN +RBV 3/wk Injections, 1-2/day pill	**Peg-IFN + RBV** 1 injection/wk, 1-2/day pills	**1 DAA+ peg-IFN + RBV** (3/day pill + 1/wk Inject. +1-2/day pill/s)	**2-3 DAAs + Peg-IFN + RB V** (1/day oral pills + 1/wk Inject. + 1/day pill	**2-3 DAAs + RB V** (1-2/day oral pill/s)	**2-3 DAAs** (1-2/day oral pill/s)
No. of Daily Pill		**RB V** (2-6/day) IFN – 3/wk	**RB V** (2-6/day) IFN – 1/wk	**PI** (8-12/day) **RBV** (2-6/day) IFN – 1/wk	**DAA** (2-3/day) **RBV** (2-6/day) IFN – (1/wk day)	**DAA** (2-3/day) **RBV** (2-6/day)	**DAA** (1-2/day)
Genotype 1	*Treatment Duration*	48 Wks	48 Wks	24-48Wks	12-24 Wks	12-24Wks	≤12Wks
	SVR Rate (HCV)	≈30%	≈40%	≈70%	≈85-90%	≈85-100%	>90%
	SVR Rate (HIV/HCV)	≈8-19%	≈30%	≈60-75%	≈80%	TBD	TBD
	Reimbursement	Yes	Yes	Yes	TBD	TBD	TBD
Genotype 2	*Treatment Duration*	24 Wks	24 Wks	N/A	12-24 Wks	12-24Wks	≤12Wks
	SVR Rate (HCV)	≈60%	≈70%	N/A	≈85%	≈95%	≈90%
	SVR Rate (HIV/HCV)	≈20%	≈60%	N/A	TBD	TBD	TBD
	Reimbursement	Yes	Yes	N/A	TBD	TBD	TBD
Genotype 3	*Treatment Duration*	24 Wks	24 Wks	N/A	12-24 Wks	12-24Wks	≤12Wks
	SVR Rate (HCV)	≈60%	≈60%	N/A	≈70%	≈60%	≈90%*
	SVR Rate (HIV/HCV)	≈20%	≈60%	N/A	TBD	TBD	TBD
	Reimbursement	Yes	Yes	N/A	TBD	TBD	TBD
Genotype 4-6	*Treatment Duration*	48 Wks	48 Wks	N/A	12-24 Wks	12-24Wks	≤12Wks
	SVR Rate (HCV)	≈30%	≈40%	N/A	≈80-95%	TBD	TBD
	SVR Rate (HIV/HCV)	≈8-19%	≈30%	N/A	TBD	TBD	TBD
	Reimbursement	Yes	Yes	N/A	TBD	TBD	TBD

**Study in combined genotypes 2 and 3*

Table 1. Current and future treatments to cure HCV

There are currently eleven drugs in phase III clinical trials for Hepatitis C. Behind these are another 22 drugs and combinations in phase II clinical trials for the treatment of Hepatitis C. However, not all of these are expected to make it to the market. Historically, only 50% of in phase II and 70% of compounds in phase III have reached the market.



Next to Market

Janssen and Medivir AB have won the race to be next to the market. They received approval for simeprevir in November 2013 in the USA and Canada. Simeprevir is a once-daily protease inhibitor used with peginterferon and ribavirin in Hepatitis C Genotype 1. A decision on this in Europe is expected in 2014.

Gilead submitted an application for approval of sofosbuvir, for use with ribavirin in Hepatitis C genotypes 2 and 3, and in combination with peginterferon and ribavirin for all other Hepatitis C genotypes. A decision on this is expected in the USA on December 8. In late October 2013, an FDA USA advisory panel voted in favour of approval of the drug in patients with Genotype 2 and 3 in combination with ribavirin. The panel also voted unanimously to approve the drug in patients with Genotype 1 and 4 in combination with ribavirin and interferon in patients who have not received prior therapy. They also appeared to support the use of sofosbuvir in patients who failed prior treatment. They have also urged Gilead to make the drug available to other companies to study in combination with other oral regimens. The FDA is not obliged to accept all the recommendations from the advisory panel but they generally do.

In Europe, sofosbuvir is expected to be licensed in early to mid-2014. However, in October 2013 the European Medicines Agency's (EMA) has given an opinion on the use of sofosbuvir, in a compassionate-use programme. It is the third time a compassionate-use programme has been assessed at the EU level. Such programmes, set up at the national level, are intended to give patients with a life-threatening, long-lasting or seriously disabling disease who have no available treatment options, access to drugs that are still under development and that have not yet been authorised. The specific conditions suggested:

- people who are actively on the waiting list for liver transplantation and require treatment to prevent graft new liver reinfection with Hepatitis C,
- people who have undergone liver transplantation and have aggressive, recurrent HCV infection resulting in progressive and worsening liver disease and are at high risk of death or decompensated liver failure within twelve months if left untreated.

Current Clinical Trials

Before you read much further about clinical trials in the coming pages there are a number of tables with summarised information from a number of the current trials that look promising. The tables are split into the key groups by genotype and where appropriate by specific treatment status (naive, null responder etc.) These may look complicated because of the way clinical trials are. It is actually pretty simple. Find the table specific to your situation and in the diagram below it gives the details of how each box works using the tables.

Study/Drug	Population/Size	Treatment Arms	SVR
The name of the study • *The combination of drugs.* • *The "+" means the study is being done with that drug, "+/-"means the study is being done in a group with that drug with and without that drug.* • *The results of the differences are shown in the Treatment Arms box.* • *If there is a set of letters and numbers, the first letters generally represent the company (e.g. ABT – ABBvie, G-Gilead, etc). The numbers represent the code within the company for the drug. Companies don't generally name drugs until they are closer to approval.* Current Phase Companies Involved	The description of what patients are in the trial. Non-cirrhotic means that people with cirrhosis have been excluded from the trial. The number of people in the trail, e.g. N=571 means 571 people in the trial.	This is a description of the different groups that the study was divided into. Example, if in the Study/Drug box it says Drug A +RBV +/-pIFN, then there will be 2 treatment arms. The first will be Drug A with Ribavirin (RBV) with pegInterferon (pIFN) and the second would be Drug A with Ribavirin (RBV) without pegInterferon (pIFN), each having their own results	These are the SVR (cure) rates. Different studies use different times as defining SVR. The standard at the moment is 24 weeks (SVR or SVR24) although this is changing. In certain boxes, it says SVR-X, this means at X (e.g. 8, 12) weeks after the end of treatment, this percentage of people had no detectable viral load and considered as cured. For the Genotype 1 tables, SVR is divided into 3 sections: 1) Overall SVR, 2) Whether or not G1a or G1b was more responsive 3) Whether or not IL28B genotype had different responses.

HCV Genotype 1 - Treatment - Naive

PegInterferon-free and PegInterferon-sparing (have to use Peg-interferon but only for the term of the new drug) combinations have been highly effective against Hepatitis C Genotype 1, regardless of subtype (G1a or G1b), IL28B genotype, and hepatitis C viral load. With these regimens, treatment duration is fixed, rather than dependent on the response to viral load and most are taken for 12 weeks. Extending treatment to 24 weeks does not appear to increase SVR rates. After 12 weeks of treatment, 56% to 100% of participants in clinical trials had non-detectable viral loads, most treatments achieved SVR rates of at least 80%. Table 2 shows the Interferon Free Regimens and Table 3 shows the Interferon Sparing Regimens. Although sofosbuvir may become a backbone for many Interferon-free regimens, the initial indication in Genotype 1 (and genotype 4) is for 12 weeks in combination with pIFN/RBV. With this regimen, cure rates reached 89% (and 80% in people with cirrhosis).

Table 2. SVR in HCV Genotype 1, Treatment-Naive: Interferon-Free Regimens

Study/Drug	Population /Size	Treatment Arms	SVR		
			Overall	HCV Subtype: 1a vs. 1b	IL28B: CC vs. non-CC
AVIATOR *ABT-450/r +/- ABT-267 +/- ABT-333 +/- RBV* Phase II AbbVie	Non-cirrhotic (N = 571)	8-week, 4-drug	**88%**	Overall: 91% vs. 98%	Overall: 95% vs. 89%
		12-week, 3-drug (no ABT-267)	**83%**		
		12-week, 3-drug (no ABT-333)	**89%**		
		12-week, 3-drug (no RBV)	**87%**		
		12-week, 4-drug	**96%**		
		24-week, 4-drug	**90%**		
AI444-040 *daclatasvir + sofosbuvir +/- RBV* Phase II Bristol-Myers	Non-cirrhotic (N = 126)	24-week, 2-drug (7-day sofosbuvir lead-in,	**93%**	No impact	
		24-week, 2-drug (no RBV)	**100%**		
		24-week, 3-drug	**100%**		
		12-week, 2-drug (no RBV)	SVR-12:**100%**		
		12-week, 3-drug	SVR-12:**100%**		
AI443-014 *daclatasvir + asunaprevir + BMS-791325* Phase II Bristol-Myers Squibb	Non-cirrhotic (N = 32)	12-week	**94%**	No impact	
		24-week	**88%**		
ELECTRON *sofosbuvir + RBV* Phase II Gilead	Non-cirrhotic (N = 25)	12-week	**84%**	No impact	
ELECTRON FDC: *sofosbuvir/ ledipasvir + RBV*	Non-cirrhotic (N = 25)	12-week	SVR-12: **100%**	No impact	
ELECTRON *sofosbuvir + GS-9669 + RBV*	Non-cirrhotic (N = 25)	12-week	SVR-12: **92%**	No impact	

Study/Drug	Population /Size	Treatment Arms	SVR		
			Overall	HCV Subtype: 1a vs. 1b	IL28B: CC vs. non-CC
LONESTAR *sofosbuvir + ledipasvir +/- RBV* Phase II Gilead	Non-cirrhotic (N = 60)	8-week, 2-drug (no RBV)	SVR-8: **95%**	No impact	
		8-week, 3-drug	SVR-8: **100%**		
		12-week, 2-drug (no RBV)	SVR-4: **100%**		
SPARE *sofosbuvir + weight-based (WB) or low-dose (LD) RBV* Phase II National Institutes of Health/Gilead	Non-cirrhotic (N = 10) All stages fibrosis (N = 50), advanced fibrosis/ compensated cirrhosis (13/50)	24-week, WB RBV	**SVR-12: 90%**	No impact (most participants were HCV genotype 1a, non-CC IL28B, high baseline HCV RNA, and African American)	
		24-week, WB RBV	SVR-12: **68%**		
		24-week, LD RBV	SVR-12: **48%**		
QUANTUM *sofosbuvir + RBV* Phase II Gilead	Non-cirrhotic (N = 50) 6% cirrhotic	12-week	SVR-12: **56%**	No impact	100% vs. 42%

Table 3. SVR in HCV Genotype 1, Treatment-Naive: Interferon-Sparing Regimens

Study/Drug	Population/Size	Treatment Arms	SVR		
			Overall	HCV Subtype: 1a vs. 1b	IL28B: CC vs. non-CC
ATOMIC *sofosbuvir + PEG-IFN/RBV* Phase II Gilead	Non-cirrhotic (N = 316)	12-week, 3-drug	**89%**	Not reported; 10/11 relapsers had non-CC genotype	
		24-week	**89%**		
		12-week, 3-drug + 12-week SOF or SOF/RBV	**87%**		
NEUTRINO *sofosbuvir + PEG-IFN/RBV* Phase III Gilead	(N = 291) 17% cirrhotic	12-week	SVR-12: **100%** Cirrhotic: **80%** Non-cirrhotic: **92%**	92% vs. 82%	98% vs. 87%

Hepatitis C Genotype 1 - Treatment - Experienced

"Quad" trials (two DAAs plus peginterferon and ribavirin) or response-guided therapy are gradually being replaced by peginterferon-free regimens in treatment-experienced people. Re-treatment with a 12 or 24 week regimen of two, three, four, or five drugs is being explored in treatment-experienced people with Hepatitis C genotype 1 (Table 4) . Most trials have been conducted in people who were unsuccessfully treated with pIFN/RBV. Two regimens (sofosbuvir and an NS5a inhibitor [either daclatasvir or ledipasvir], with or without ribavirin) have been studied in people who were unsuccessfully treated with pIFN/RBV and an Hepatitis C protease inhibitor. Cure rates have ranged from a dismal 11% to 100% with most regimens having SVR's around 90% of treatment-experienced. The majority with poor indicating factors such as IL28B CT or TT genotype, Hepatitis C genotype 1a, and high Hepatitis C viral loads.

Table 4. SVR in HCV Genotype 1, Treatment-Experienced: Interferon-Free Regimens

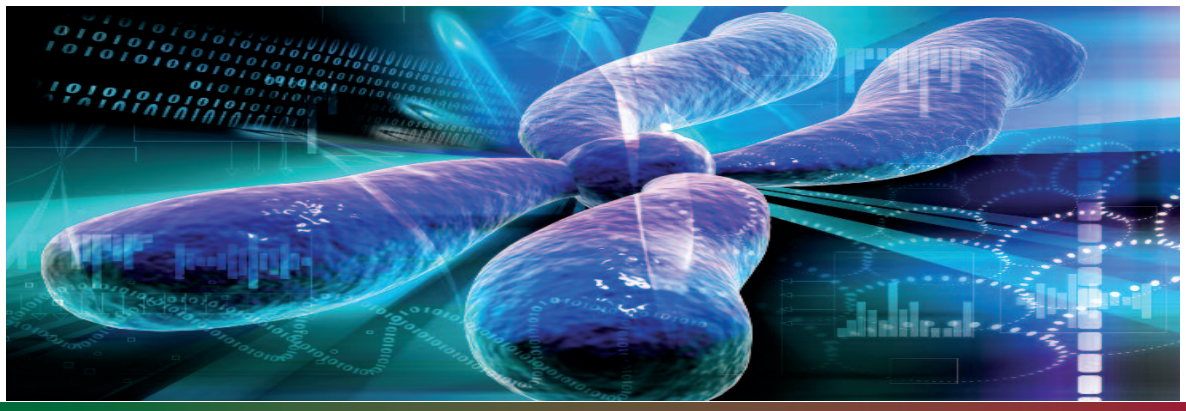
Study/Drug	Population/Size	Treatment Arms	SVR		
			Overall	HCV Subtype: 1a vs. 1b	IL28B: CC vs. non-CC
AVIATOR *ABT-450/r + ABT-267 +/- ABT-333 + RBV* Phase II AbbVie	Non-cirrhotic, null responders (N = 133)	12-week, 3-drug (no ABT-333)	**89%**	93% vs. 97%	94% vs. 100%
		12-week, 4-drug	**93%**		
		24-week, 4-drug	**95%**		
AI444-040 *daclatasvir + sofosbuvir +/- RBV* Phase II Bristol-Myers Squibb/Gilead	Non-cirrhotic, prior boceprevir or telaprevir use (N = 41)	24-week, 2-drug (no RBV)	SVR-12:**100%**	No impact	
		24-week, 3-drug	**100%**		
COSMOS (Interim data) *simeprevir + sofosbuvir +/- RBV* Phase II Janssen /Gilead	Non-cirrhotic, null responders (N = 80) 100% non-CC genotype	12-week, 2-drug	SVR-8: **92.9%**	No impact	N/A
		12-week, 3-drug	SVR-8: **96.3%**		
		24-week, 2-drug	SVR-8: **100%**		
		24-week, 3-drug	SVR-8: **66.7%**		
ELECTRON *sofosbuvir + RBV* Phase II Gilead	Non-cirrhotic, null responders (N = 10)	12-week	**11%**	No impact	
ELECTRON FDC: *sofosbuvir/ ledipasvir + RBV*	Non-cirrhotic, null responders (N = 10)	12-week	SVR-4: **100%**	No impact	
LONESTAR (Interim data) *sofosbuvir + ledipasvir +/-RBV* Phase II Gilead	Non-cirrhotic, prior boceprevir or telaprevir use (N = 40)	12-week, 2-drug (no RBV)	SVR-4: **95%**	No impact	
		12-week, 3-drug	SVR-4: **95%**		
QUANTUM (Retreatment) *sofosbuvir + RBV* Phase II Gilead	N = 105 10% cirrhotic in control or discontinued arms	24-week, 2-drug retreatment	SVR-12: **66%**	71% vs. 48%	84% vs. 63%

Hepatitis C Genotypes 2 and 3

Until the DAA era, genotypes 2 and 3 were considered easily cured. It is easier to achieve an SVR with Genotype 2 regardless of cirrhosis or prior treatment failure. However, Genotype 3 is proving to be a challenge. Only one peginterferon-free regimen (sofosbuvir plus daclatasvir), with or without ribavirin—has yielded cure rates above 65%, after 24 weeks of treatment. Adding pIFN to a 12-week course of sofosbuvir and ribavirin seems to boost SVR rates. Adding peginterferon to sofosbuvir and ribavirin for 4 or 8 weeks pushed cure rates to 100% in Hepatitis C Genotype 3. (Table 5)

Table 5. SVR in HCV Genotypes 2 and 3

Study/Drugs	Group/Size	Genotype	Treatment Arms	SVR
AI444-040 *daclatasvir + sofosbuvir +/–RBV* Phase II Bristol-Myers Squibb/Gilead	Treatment-naive, non-cirrhotic (N = 44)	Genotypes 2 and 3	24-week, 2-drug (7-day sofosbuvir lead-in, no RBV)	**88%**
			24-week, 2-drug (no RBV)	**100%**
			24-week, 3-drug	**93%**
COMMAND GT 2/3 *daclatasvir + PEG-IFN/RBV vs. placebo + PEG-IFN/RBV* Phase II Bristol-Myers Squibb	Treatment-naive, 20% cirrhotic (G3 only) (N = 151)	Genotype 2	12-week	**88%**
			16-week	**83%**
			placebo	**63%**
		Genotype 3	12-week	**69%**
			16-week	**70%**
			placebo	**59%**
ELECTRON *sofosbuvir + RBV + 0, 4, 8, or 12 weeks of pIFN vs. sofosbuvir* Phase II Gilead	Treatment-naive, non-cirrhotic (N = 60)	Genotypes 2 and 3	8-week, 3-drug	**100%**
			12-week, with 4-week pIFN	**100%**
			12-week, with 8-week pIFN	**100%**
			12-week, 3-drug	**100%**
			12-week, no PEG-IFN	**100%**
			12-week, sofosbuvir only	**60%**



Study/Drugs	Group/Size	Genotype	Treatment Arms	SVR
				Non-cirrhotic: 71%
FUSION *sofosbuvir + RBV* Phase III Gilead	Treatment-experienced, 34% cirrhotic (N = 201)	Genotype 2	12-week	SVR-12: **86%**
				Cirrhotic: 60%
				Non-cirrhotic: 96%
			16-week	SVR-12: **94%**
				Cirrhotic: 78%
				Non-cirrhotic: 100%
		Genotype 3	12-week	SVR-12: **30%**
				Cirrhotic: 19%
				Non-cirrhotic: 37%
			16-week	SVR-12: **62%**
				Cirrhotic: 61%
				Non-cirrhotic: 63%
POSITRON *sofosbuvir + RBV* Phase III Gilead	Treatment naive, interferon-ineligible, -intolerant, and -unwilling, 15% cirrhotic (N = 207)	Genotype 2	12-week	SVR-12: **93%**
				Cirrhotic: 94%
				Non-cirrhotic: 92%
		Genotype 3	12-week	SVR-12: **61%**
				Cirrhotic: 21%
				Non-cirrhotic: 68%
PROTON *sofosbuvir + PEG-IFN/RBV* Phase II Gilead	Treatment-naive, non-cirrhotic (N = 25)	Genotypes 2 and 3	12-week	SVR-12: **92%**

Hepatitis C Genotypes 4 - 6

Ongoing trials are exploring different regimens in Genotype 4. Final data is available, after 12 or 24 weeks of treatment with sofosbuvir plus peginterferon and ribavirin. Only 39 people with genotype 4 were treated. After 24 weeks (SVR) the results were 82% and after 12 weeks (SVR-12) were 96%. To date, sofosbuvir and pIFN/RBV is the only regimen to have been studied in Hepatitis C Genotypes 5, albeit in only 13 people, one with genotype 5.

Table 6. SVR in HCV Genotypes 4, 5, and 6, Treatment-Naive: Interferon-Sparing Regimens

Study/Drug	Population	HCV Genotype/Size	Duration	SVR
ATOMIC *sofosbuvir + PEG-IFN/RBV* Phase II Gilead	Non-cirrhotic	Genotype 4 (N = 11)	24-week	**82%**
		Genotype 6 (N = 6)		**82%**
NEUTRINO *sofosbuvir + PEG-IFN/RBV* Phase III Gilead	Liver histology not available	Genotype 4 (N = 28)	12-week	SVR-12: **96%**
		Genotype 5 (N = 1)		SVR-12: **100%**
		Genotype 6 (N = 6)		SVR-12: **100%**

HIV/Hepatitis C Co/Infection

Hepatitis C co-infection increases AIDS-related, liver-related, and all-cause mortality among people with HIV, despite the use of antiretroviral therapy (ART). The incidence of Hepatitis C related complications has been rising among HIV/Hepatitis C co-infected people. Clearly, people who are HIV/Hepatitis C co-infected should be a priority population for DAA trials, since they are at risk for more rapid Hepatitis C progression. Although companies stand to benefit from supporting these trials, development of peginterferon-free trials has been lagging. As of May 2013, only one peginterferon-free trial (sofosbuvir and ribavirin) was open to HIV/Hepatitis C-coinfected people. Ongoing trials with simeprevir, faldaprevir, and daclatasvir are peginterferon-based. However, the good news is that, initial reports suggest that HIV does not appear to be a significant factor when a DAA is added to peginterferon and ribavirin. This has been supported by data from trials of telaprevir-based treatment, as well as interim reports from 2 other trials, STARTVerso 4 (faldaprevir-based treatment) and the TMC435-C212 (simeprevir-based treatment) study.

Interferon Sparing - Faldaprevir plus PEG-IFN/RBV

STARTVerso 4 is an ongoing, 308-person, phase III trial of faldaprevir plus peginterferon and ribavirin in HIV/Hepatitis C co-infected people with Hepatitis C Genotype 1 who were treatment-naive or relapsers. 17% were cirrhotic. No HIV virological breakthrough occurred. By week 12, Hepatitis C viral load was undetectable in 82% of treatment-naive participants and 91% of relapsers. The most common side effects were nausea, fatigue, diarrhoea, and headache. Serious adverse events (<1%) reported were fever, abdominal pain, rash, vomiting, dehydration, gastroenteritis, anemia and neutropenia. Three deaths occurred in the study, two were not considered related to the study drug, and the third was due to drug reaction with eosinophilia and is currently under review.

Interferon Sparing - Simeprevir plus PEG-IFN and RBV

TMC435-C212 is an ongoing Hepatitis C treatment trial in 106 treatment-naive or treatment-experienced people co-infected with HIV and Hepatitis C Genotype 1. No HIV virological breakthrough occurred. Interim results are promising. SVR-12 was 75% (9 of 12). Relapse has been reported only in people with Hepatitis C Genotype 1a. At the time of analysis, 64% of null responders remained on treatment. The safety of this study is described as similar to that reported in Hepatitis C mono-infection, with four people discontinuing for adverse events. Common side effects were fatigue, headache, nausea, pruritus, and rash.

A Novel Approach - MicroRNAs

MicroRNAs are present in human cells and their job is to regulate gene expression. MicroRNA 122 (miR-122) is found in liver cells and it binds to the Hepatitis C virus, stabilizing it and stimulating viral replication. A drug targeting miR-122, called miravirsen, is being studied in Hepatitis C Genotype 1 (although it is useful for all genotypes). Miravirsen has potential as a supplemental therapy and could be administered once monthly and is not expected to have significant drug-drug interactions with DAA's or other commonly used medications.

Cirrhosis

Hepatitis C patients awaiting liver transplants are in need of treatment but often cannot tolerate interferon-based therapy. On the other hand left untreated, Hepatitis C almost always infects the new liver soon after transplantation, which can lead to cirrhosis, graft failure and death. Demonstrating that DAAs were effective in null responders was the first area for peginterferon-sparing and peginterferon-free regimens. But cirrhosis is the true test with a need for Hepatitis C treatment that is safe and effective for people with cirrhosis and will work at least as well for everyone else. Prioritising people with more serious liver damage for Hepatitis C treatment is both ethical and sensible. This may prevent transplantation and death from liver disease. Yet patients with advanced liver disease have been underrepresented in, or excluded from, many clinical trials. Drugs are being brought to market with limited data in people with cirrhosis, who are most likely to be treated first. Serious side effects and fatalities have been reported from trials of boceprevir- and telaprevir-based regimens in people with compensated cirrhosis. A phase II trial, SOUND-C, is an example of a proactive approach to include this group, since it included a subset of 33 people with compensated cirrhosis and reported SVR rates in this group as high as 67%.

Pre-Transplant

A study was carried out on the use of sofosbuvir and ribavirin to prevent Hepatitis C recurrence following liver transplantation. This study enrolled 61 people, mostly in the US. Participants had compensated liver disease and were listed for transplantation due to hepatocellular carcinoma (HCC), a type of liver cancer. People with Hepatitis B or HIV co-infection, decompensated cirrhosis or kidney impairment were excluded. The original regimen was 24 weeks but this was later extended to 48 weeks. The last dose was taken on the day of transplantation. They received standard immunosuppressive therapy to prevent rejection of the new liver. A total of 41 participants underwent transplantation with undetectable viral load while three people did so while viral load was still detectable. Ten discontinued treatment, four finished treatment but were still awaiting transplants and one was still on therapy while waiting.

Hepatitis C viral load declined rapidly after starting sofosbuvir and ribavirin. Most patients who received treatment for any duration (93%) or for at least 12 weeks (91%) had an undetectable viral load at the time of transplantation. Among those with undetectable Hepatitis C at transplantation, 64% maintained viral suppression at 12 weeks post-transplant. People who did not experience Hepatitis C recurrence had undetectable viral load for a median of 95 days before transplantation compared with just 5.5 days for those who did have a recurrence. Only 1 patient had a recurrence after having an undetectable viral load for 30 days or more. Sofosbuvir and ribavirin was generally safe and well tolerated in this difficult-to-treat population. There were 11 serious adverse events. None of which were considered related to sofosbuvir. There were two discontinuations due to adverse events (3%). Three people died before transplantation and five afterwards. The most common side-effects were fatigue (38%), anaemia (23%) and headache (23%).

Post TransIplant

The second study, looked at sofosbuvir and ribavirin for treatment of Hepatitis C recurrence after liver transplantation. This included 40 participants in France, Germany, New Zealand, Spain and the US. Participants had undergone liver or combined liver and kidney transplants between six months and 12 years (median four years) before and did not experience organ rejection or have signs of liver decompensation. Participants were treated with sofosbuvir for 24 weeks. They also started with a low dose of ribavirin which was gradually increased based on tolerability (determined by haemoglobin levels). Hepatitis C viral load again declined rapidly after starting therapy. At week 4 and at the end of treatment all participants had undetectable viral load. Four weeks after completing treatment 77% had no detectable viral load. This is a promising result, but too early to determine as a cure as relapse has been seen after this point in other sofosbuvir studies. No interactions were reported between sofosbuvir and any immunosuppressant agents including tacrolimus (used by 70%), mycophenolate mofetil (35%), prednisone (28%) or cyclosporin (25%), though four people did increase their tacrolimus dose while on sofosbuvir.

Toward Collaboration

Financial considerations play a significant role in Hepatitis C drug development. Competition for market share is fierce, since experts estimate that the Hepatitis C market in Japan, the United Kingdom, Germany, France, Italy, Spain, and the United States will reach US$14-20 billion by 2018. Most pharmaceutical companies are developing in-house combinations to avoid sharing the market. As a result, only three trials have combined DAAs from different companies. Sofosbuvir (Gilead) has been paired with daclatasvir (BMS) and simeprevir (Janssen). Sofosbuvir and daclatasvir have been tested with or without Ribavarin and results were spectacular. SVR rates ranged from 88-100% after 12 or 24 weeks of treatment, regardless of treatment history, ribavirin use, Hepatitis C Genotype or subtype, IL28B genotype, or treatment duration. The study included 170 non-cirrhotic, treatment-naive participants with Hepatitis C Genotypes 1, 2, and 3, and 41 treatment-experienced participants with Hepatitis C Genotype 1.

Another trial, uses a combination of simeprevir and sofosbuvir (next two to market) for 12 or 24 weeks, with or without ribavirin. This includes two groups of null responders with Hepatitis C genotype 1. Group 1 were people with very mild to moderate liver scarring and group 2 were people with extensive liver scarring and cirrhosis. Although most of group 1 had poor indicating factors (IL28B non-CC genotype and Hepatitis C genotype 1a), early results were very good 8 weeks after treatment finished, 96% in the sofosbuvir/simeprevir/RBV arm, and 92% in the sofosbuvir/simeprevir arm achieved an SVR. There were no discontinuations, but two relapses occurred, one in each arm. So far, 24 people have been followed until 12 weeks after treatment, and 100% remain undetectable. The regimen was safe and tolerable. The second group was fully enrolled as of March of 2013 and is still under investigation. Unfortunately, it is likely that Gilead's partnership with Janssen or BMS will be short-lived, regardless of the final results of either study as they are developing their own NS5A inhibitor, ledipasvir, possibly in a single pill with sofosbuvir.

Simeprevir and daclatasvir are being tested, with or without RBV, for 12 or 24 weeks (plus an optional extra 24 weeks of pIFN/RBV if needed), in an ongoing trial of 180 treatment-naive and prior null responders with Hepatitis C Genotype 1, including people with cirrhosis. Off-label use of these drugs may be possible, although it will be difficult to persuade health authorities to pay for drugs from two separate regimes to be used at the same time in the same patient unless this was a recognised and licenced combination.

Summary

Treatment for Hepatitis C virus in the future should be simpler, shorter, and more effective. All-oral combinations of direct-acting antivirals (DAAs) have pushed SVR rates in Hepatitis C genotype 1 to over 90%. However, we are far from having a single-tablet regimen suitable for everyone. Peginterferon-free treatment is less effective against Hepatitis C Genotype 3, and very little is known about treating genotypes 4, 5, and 6 with DAA's.

More information is needed on the safety, efficacy, and tolerability of DAA's in those likely to be prioritized for Hepatitis C treatment, such as HIV co-infection and cirrhosis. Despite dozens of ongoing trials, data on DAA based regimens in people with cirrhosis, especially those who are treatment-experienced are limited. As of May 2013, there was only one peginterferon-free trial available to people co-infected with HIV and Hepatitis C. Some key points:

- New Direct Acting Antivirals (DAA') are a very exciting and real prospect but it will be some time before we see a lot of them.
- The next DAA to market in Europe should be in early 2014 and this is for all genotypes. There will be two more coming later in 2014 and early 2015 but these are just for Genotype 1.
- More work needs to be done on patients who will be prioritised such as HIV co-infection, cirrhosis and pre and post liver transplantations.

The Irish Haemophilia Society will continue to monitor these developments and keep you informed in as timely a manner as possible about changes and updates in upcoming newsletters. We will also be actively advocating for the inclusion of people with haemophilia in clinical trials and early access programs for those that are in most need of treatment. We will continue to make submissions on behalf of people with haemophilia to the HTA body who assess the cost effectiveness and recommend whether these new drugs should be re-imbursed. If these new products follow the same path as the last two DAA's the next new drug in Ireland for Hepatitis C could be assessed and depending on the recommendation be available in second half of 2014.

ICORN and the Consultative council on Hepatitis C

The Statutory Consultative Council on Hepatitis C was established in 1996 and was set up to provide input and recommendations to the health authorities on all aspects of treatment and care for persons who were infected with Hepatitis C via blood or blood products supplied by the state. The Council initially had representatives from the four patient organisations whose members were infected with Hepatitis C via blood products. These were: 'Positive Action' representing women who were infected via anti D, 'Transfusion Positive' representing people infected via blood transfusion, the 'Irish Kidney Association' representing those who were infected via renal dialysis and of course the 'Irish Haemophilia Society' representing those infected by blood products or factor concentrates. The initial Council had two representatives each from Positive Action and Transfusion Positive with one each from the Irish Kidney Association and the Irish Haemophilia Society. The Council also had hepatologists, a nurse a representative from the HSE and a general practitioner and was chaired by a Hepatologist, Dr. Liz Kenny. The Council has been inactive for the past two years and the clinical/patient organisation interface was not working.

As part of the conditions attached to the reimbursement of the new therapies for Hepatitis C in 2012, the Health Technology Assessment recommended that the clinicians establish a separate clinical group - the Irish Hepatitis C Outcomes Research Network (ICORN). The clinicians established this group in 2012. It consists of the Hepatologists and infectious disease consultants from the hospitals where there are specific hepatology centres. In addition, the group has representatives from the Virus Reference Laboratory, the HSE (Michele Tait), Hepatology nurses (Helena Irish) and a representative of the patient organisations (Brian O'Mahony). The ICORN group monitors the outcome of treatment, has established a treatment registry and collectively review and decide on best practice in treatment and dealing with side effects and laboratory parameters. It is a very welcome addition to the management of Hepatitis C in Ireland and allows for more collaborative and cohesive thinking between the clinicians on a national basis. A separate article in this edition (see page 15) on ICORN is included written by Professor Suzanne Norris, Chair of the ICORN Group.

The Consultative Council on Hepatitis C has now been established in a more slimmed down format with eight members - two each from Positive Action, Transfusion Positive, and the Irish Haemophilia Society and one from the Irish Kidney Association and is chaired by Michele Tait from the HSE. The Society is represented on the new Council by Brian O'Mahony and Anne Duffy. The first meeting was held in July and meetings will take place six times per year. The next stage of the process is for the Council to strategically plan the work for the coming three years. I hope that we can concentrate on substantive policy issues which will have a real bearing on the ability of those with Hepatitis C to live with the condition or ideally be supported through treatment to clear the virus. Over the coming months, I also hope that regular liaison with the ICORN group can facilitate separate but complementary programmes of work to benefit people with Hepatitis C.

It is the intention to have the chair of ICORN invited to attend some Council meetings when specific clinical areas are on the agenda and to receive updates on the work and approach of ICORN. This communication will also be facilitated by the fact that Council chair Michele Tait and I both are members of ICORN in addition to the Council. Patient education and education, via materials and conferences, will be key areas of work. The specific areas the Council will work on in the coming years will include:

- Patient friendly information on treatment.
- Advocacy for requirements of those with Hepatitis C via blood or blood products.
- Monitoring of review and working of entitlements under HAA card and Travel and Life Insurance Schemes.
- Agree collaboration and liaison with ICORN and National Strategy Group (which will be looking at issues such as prevention of new cases of Hepatitis C in the population).
- Data collection (research) by individual patient organisations - co-operation and collaboration where possible.
- Data collection - setting priorities for HPSC database which collects data on the progression of Hepatitis C in those who were infected via blood or blood products.

Brian O'Mahony,
Chief Executive.

ICORN Group

Hepatitis C is a world-wide public health problem resulting in a significant impact on healthcare resource utilisation and costs. In Ireland, 9,282 cases of Hepatitis C were notified between 2004 and 2010. However, the true prevalence of Hepatitis C in Ireland is unknown. In a recent paper linking notifications to virology laboratory results, Thornton et al estimated that there are approximately 30,000-50,000 patients infected with chronic Hepatitis C in Ireland, with the majority of infected patients undiagnosed. Of the 6 known Hepatitis C genotypes, genotype 1 is the most common genotype, accounting for approximately 55% of infections in Ireland. Complications of chronic Hepatitis C infection include to compensated cirrhosis, decompensated liver disease, hepatocellular carcinoma and death. Hepatitis C infection therefore represents a significant burden of care to the Irish healthcare system. In 2012, patients infected with Hepatitis C virus Genotype 1 were provided with the option of enhanced therapeutic outcome with the availability of directly-acting antiviral agents (DAA's) as add-on therapy to a backbone to dual therapy with pegylated interferon and ribavirin. Efficacy data from randomised controlled trials reported significantly improved cure rates in terms of achievement of a sustained viral response (SUR) in both treatment naïve and treatment experienced patients. Clinical efficacy and economic outcome data are currently derived from randomised controlled trials, however, is recognised that there is a need to assess the effectiveness of the agents in the real world setting.

Given the complexity of protease inhibitor-based treatment paradigms, and the requirement for a co-ordinated national approach to the introduction of the new therapeutic agents, the Irish Hepatitis C Outcomes and Research Network (ICORN) was established in February 2012. This national network comprises hepatologists from all seven national hepatology centres, consultants in infectious diseases, virologists, epidemiologists, scientists, experts in biostatistical analysis, the H.S.E., and patient organisations. This unique cluster of clinical and research expertise is united in realising the underlying aim of ICORN – enhancing the quality of care for all patients treated with protease inhibitors through the development of a national governance structure for antiviral stewardship. Through the establishment of a Clinical Advisory Group, ICORN developed national HCV treatment guidelines in September 2012, which is informing the rollout of the national Hepatitis C Protease Inhibitor Treatment Programme. Additionally, ICORN members recognised the need for a national research database to prospectively collect and collate data on treated patients to allow true clinical and economic outcomes to be assessed following the introduction of these agents in routine clinical practice, without the strict inclusion/exclusion criteria applied in the clinical trial setting. Consequently, the ICORN Hepatitis C Treatment and Outcomes Registry was developed in 2012, and a prospective, longitudinal, observational outcomes research study for patients with Hepatitis C treated with direct-acting antiviral agents commenced.

Data gathered prospectively in this Hepatitis C observational outcomes study, under the stewardship of ICORN, will provide real world evidence of the clinical effectiveness, economic impact and safety of triple therapy regimens when used in routine clinical practice, with the aim of informing clinical practice and refining health policy strategies for the Irish hepatitis C cohort of patients. This project will additionally fulfil several of the recommendations outlined in the National Hepatitis C Strategy 2011-2014 document.

Professor Suzanne Norris,
Consultant Hepatologist.

Irish Haemophilia Society,
First Floor, Cathedral Court,
New Street, Dublin 8.
Tel: 01 6579900 Fax: 01 6579901
Email: info@haemophilia.ie Website: www.haemophilia.ie