Positive News

Information Magazine for people with Hepatitis C and HIV

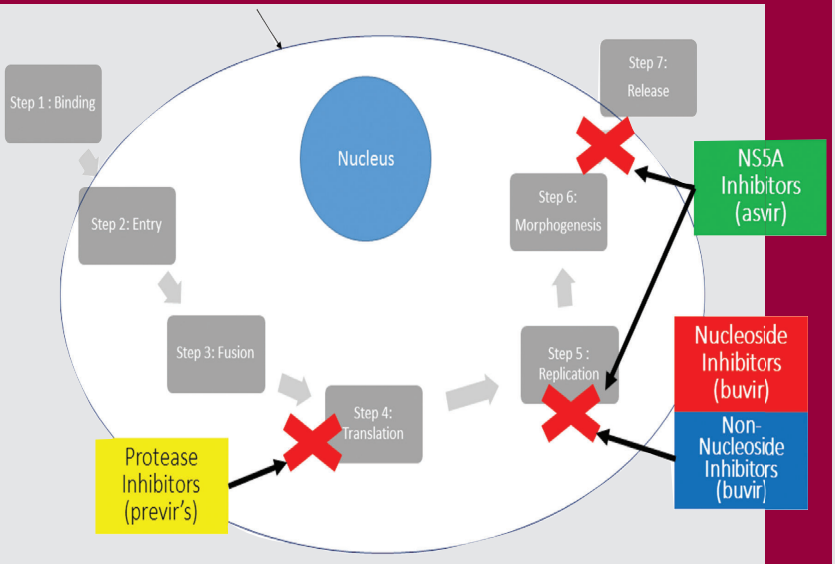
The Irish Haemophilia Society

Representing people in Ireland with haemophilia and related bleeding disorders

NEW DAA-Y'S DAWN FOR HEPATITIS C TREATMENT

We have been talking about 'Direct Acting Antivirals' (DAA's) for the last few years. These antivirals have been around for a relatively long time in HIV, and we have seen the first two for hepatitis C (Telaprevir and Boceprevir) come to the market in Europe in 2011. The latest one is Sofosbuvir (brand name Sovaldi®) which was licensed in January 2014, with Simeprevir (brand name Olysio®) licensed in May 2014 for Genotype 1 and 4 and Daclatasvir which is due to be licensed in September. With several more due out next year, all of which are showing impressive 'Sustained Virological Response's' (SVR's), it is important to know why these treatments are different to pegInterferon and Ribavirin.

Hepatitis C is a virus, and like all viruses there is a set pathway that a virus needs to take in order to infect a cell and move on to the next cell to spread the virus. These new drugs (as the name suggests) directly acts on this pathway and stops the virus completing that step, and moving on to the next. However, in order for a virus to continue to live it learns to evolve extremely quickly. With this in mind the best way stop the virus, is not a single pronged attack, but a multipronged attack stopping several points in the pathway of the virus, at the same time. There are three main types of DAA's being created:Protease Inhibitors, Nucleoside/Non-Nucleoside Inhibitors and NS5A inhibitors.



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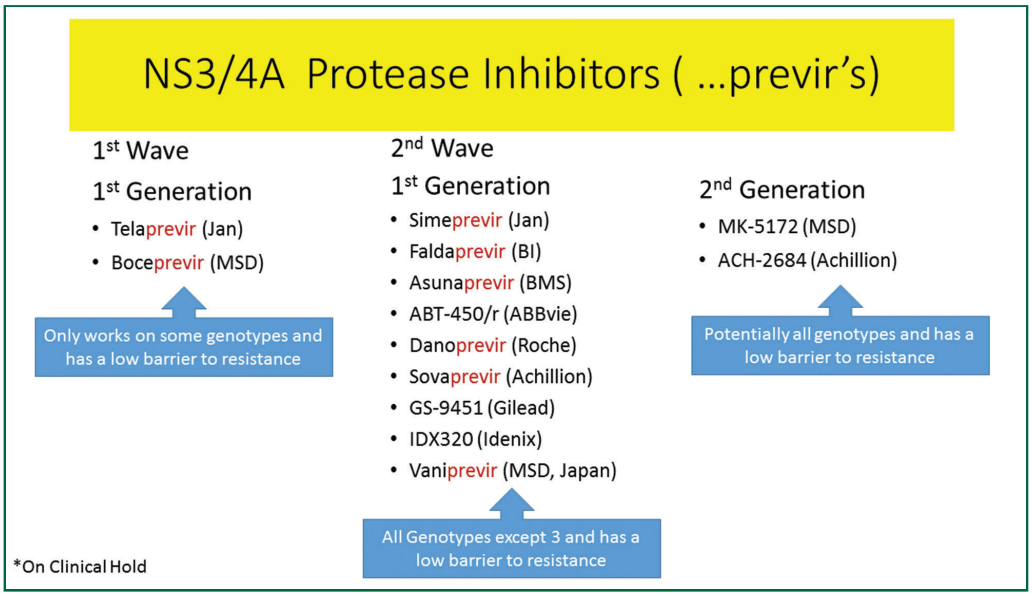
Edition: June 2014

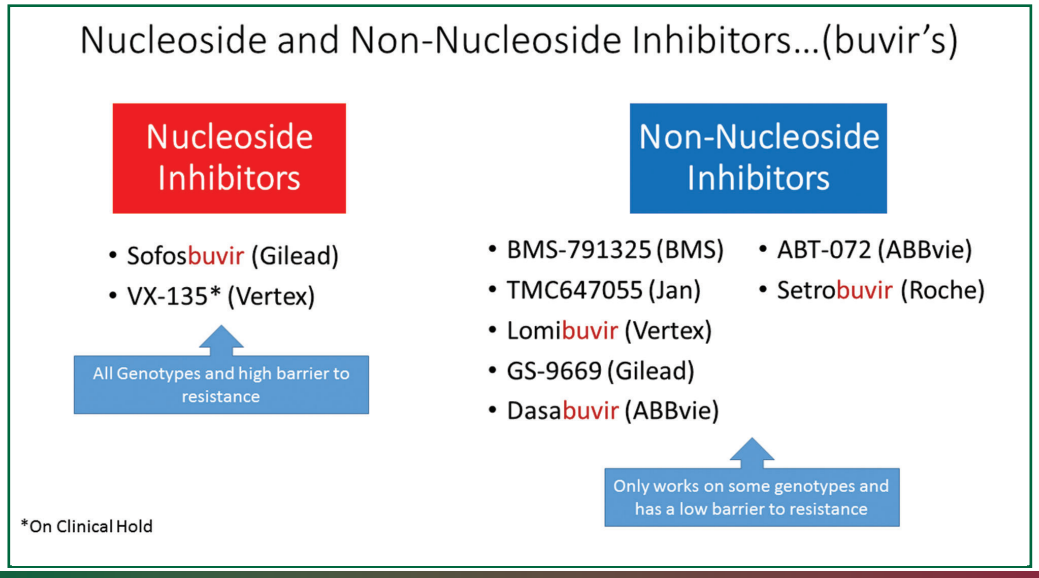
PROTEASE INHIBITORS

Protease Inhibitors stop what is known as the translation step. When the virus gets into the cell it needs to hijack the factories in the cell that make proteins, so they can use them to make their own proteins in order to multiply. Protease Inhibitors, recognisable by "previr" at the end of their name, stop the virus using the factories and prevent the hijack. There are two main problems with stopping this step on its own. Firstly, these drugs have a low barrier to resistance and secondly they have narrow genotype coverage. Using the same analogy of an army division, in the first case the army effectively only attack the virus at the gates to the factories and in time when the virus evolves and gets in over the fences and the 'Protease Inhibitors' are effectively useless. In the second case they don't recognise other Genotypes so when they turn up at the gates the Protease Inhibitors let them pass through. There are two generations of 'Protease Inhibitors', with the second generation being better at preventing more than one Genotype from carrying out this step.



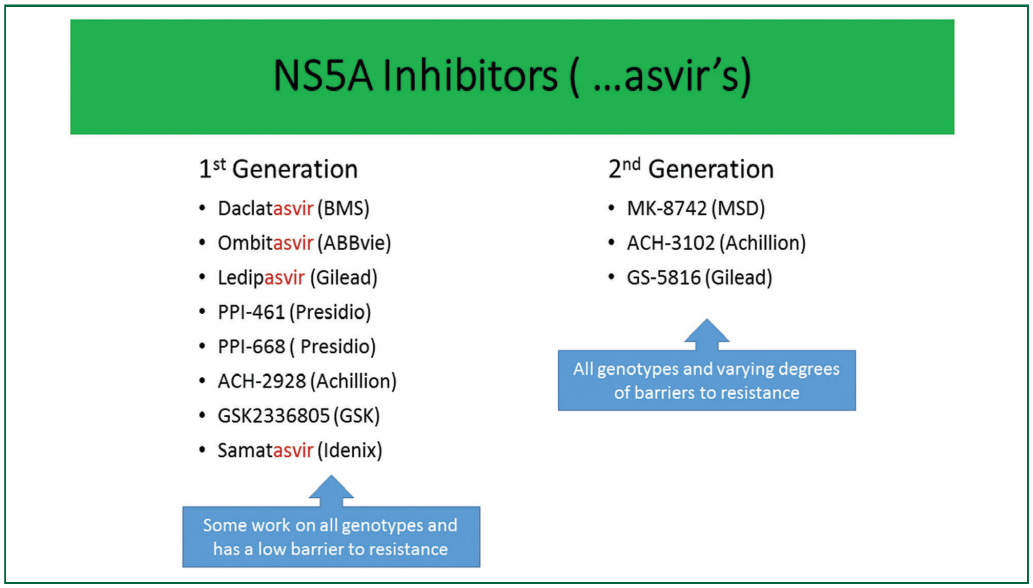
NUCLEOSIDE/NON-NUCLEOSIDE INHIBITORS

These drugs stop the replication step. When a virus is replicating, it splits itself in half and then uses proteins it would have created in the factories to make it whole again. This army division, recognisable by the "buvir" at the end of its name, effectively wrap themselves around the virus like a strait-jacket and stops the split. As with the Protease Inhibitors, the same two issues need to be considered (barrier to resistance and recognising all Genotypes). The 'Nucleoside Inhibitors' recognise all of the Genotypes. They also have a high barrier to resistance so if the virus gets out of the strait-jacket, and changes, this group of drugs are still good at stopping the replication. The 'Non-Nucleoside Inhibitors' on the other hand only recognise certain Genotypes and have a lower barrier to resistance, i.e when the virus changes these are no longer useful.



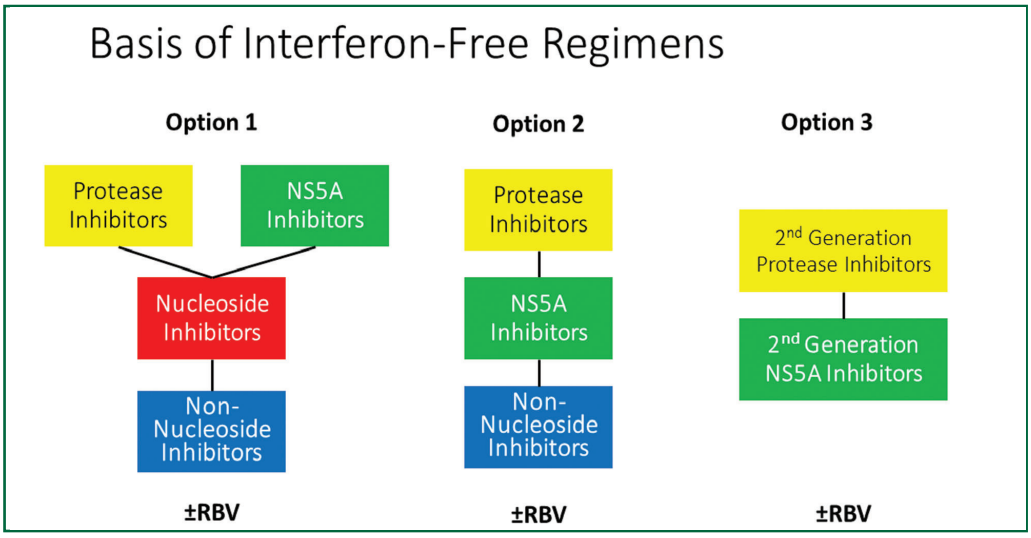
NS5A INHIBITORS

These drugs multitask. They prevent the replication step and they prevent the release of new viruses. NS5A Inhibitors are recognisable by "asvir" at the end of the name. There are two generations of these drugs. In 1st generation, some work on all Genotypes but have a low barrier to resistance and in the 2nd generation they work on all Genotypes, with varying degrees of preventing resistance.



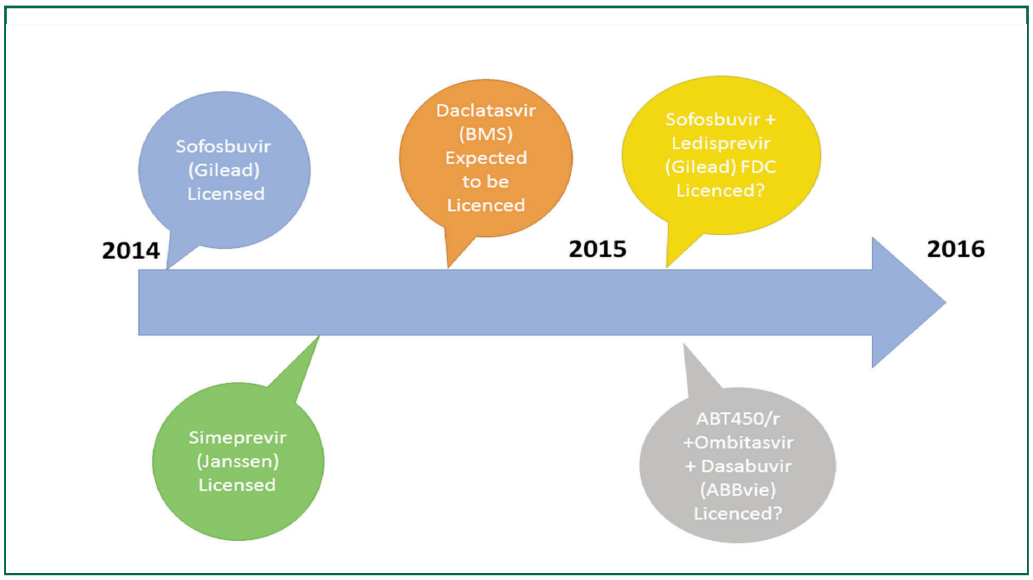
STRATEGIC STRIKE

In 2011, we saw the first Protease Inhibitors (Telaprevir and Boceprevir). In January of 2014, the first Nucleoside Inhibitor (Sofosbuvir) was licenced. As of April 2014, for all Genotypes except Genotype 2 pegInterferon (pIFN) and Ribavirin (RBV) are still being used. This is because on their own a DAA does not act fast enough and allows the virus to adapt to the attack from these new drugs. Using the army analogy again, pIFN ("Napalm" - barrels of petrol) and RBV (unguided missiles) are dropped in to destroy as much of the virus as it can so what's left of the virus doesn't have time to regroup before the DAA attacks. As we have seen with the old treatments, the blast all insight approach doesn't just affect the virus but the entire surrounding environment resulting in a number of side effects. The new plan is significantly more elegant. When a single DAA (strike team) is used on its own to attack one step in the pathway, the virus is able to adapt quickly and get around the attack. The new plan then is to use a combination of DAA's (multiple strike teams) with a high speed co-ordinated strike at key points in the virus's pathway take out the existing virus before it knows what hit it. Currently there are 3 combinations being developed to carry out these strikes, which are shown below and getting SVR rates in the 90-100% range. Whilst the pIFN has been removed there is still some discussion for the need for RBV which is currently being assessed.



INTRODUCTION TO GENOTYPES

In 2011, we saw 2 drugs come on the market (Telaprevir and Boceprevir). These still had to be used with pegInterferon and Ribavirin. In January 2014, Sovaldi® (Sofosbuvir) by Gilead received a licence for all Genotypes in Europe and in May, Olysio® (Simeprevir) by Janssen, received a licence for Genotype 1 and 4. A third drug, Daclatasvir by Bristol Myers Squibb is expected to be licenced for all Genotypes in September 2014. These drugs can be used with pegInterferon and Ribavirin with varying degrees of effectiveness similar or improving on the current treatments. However, taking a leaf out of the HIV treatment book, these drugs can be used in combinations with each other without pegInteferon to improve results. They are still combined with Ribavirin but there is potential that this too will be dropped from the hepatitis C treatment regimens in the near future. The following pages are a summary of current and future treatments in hepatitis C by Genotype. For a more detailed version, please visit our website: www.haemophilia.ie



GENOTYPE 1

Genotype 1 has traditionally been the most difficult genotype to treat in the hepatitis C group. It is also currently the most prevalent in the developed world. As a result it has received a lot of attention in the past few years and new drugs for the treatment are coming out at an extremely fast pace with the vast majority being highly effective achieving results in excess of 90% of patient. The other point to note is that this effectiveness is not just seen in the easy to treat groups. These drugs are as efficacious in people with rapid progression, cirrhosis and people who have previously failed older treatments.

Genotype 1 - (2014)

In the NEUTRINO Phase III trial in treatment-naïve patients, with Sofosbuvir and pegInterferon (pIFN) and Ribavirin for 12 weeks, the overall SVR rate was 89% (259/291). 92% (207/225) for subtype 1a and 82% (54/66) for subtype 1b. Patients with cirrhosis had a lower SVR rate than those without cirrhosis (80% vs. 92%, respectively).

In the QUEST-1 and QUEST-2 Phase III clinical trials in previously untreated patients, with Simeprevir and pegInterferon (pIFN) and Ribavirin (RBV) , the overall SVR rates were 80% (210/264) and 81% (209/257), respectively. In a pooled analysis of both trials, patient's subtype 1b achieved an SVR in 85% of cases (228/267). In patients with subtype 1a, 84% (138/165) achieved an SVR. An SVR was achieved in 84% (317/378) of patients with none or mild fibrosis, 73% (60/82) of patients with moderate fibrosis, and 60% (29/48) of patients with cirrhosis. In previously untreated, HIV co-infected patients in the C212 study, with Simeprevir and pegInterferon (pIFN) and Ribavirin (RBV), SVR was achieved in 79% of patients (42/53). In previously treated patients who relapsed after treatment, SVR was achieved in 86% (128/149) of subtype 1b patients and in 70% (78/111) of subtype 1a patients.

In C212, the SVR rate in HIV-co infected patients who were previously treated and relapsed was 87% (13/15). Licencing was granted in May 2014 for Europe for Genotypes 1 and 4.

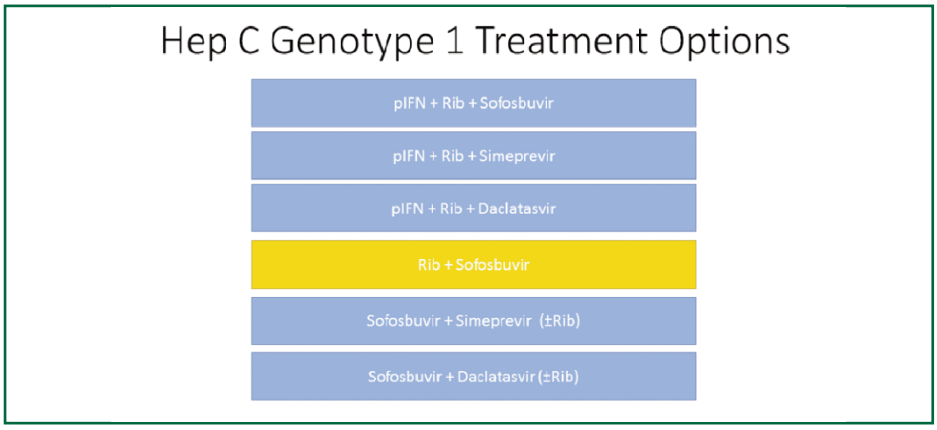
In the Phase IIb COMMAND-1 study in Genotype 1 previously untreated patients, with Daclatasvir and pegInterferon (pIFN) and Ribavirin (RBV), results has shown SVR rates of 87% (27/31) in subtype 1b subjects and 58% only (66/113) in subtype 1a patients. Although this combination is theoretically effective, there is little data and further information is pending in on-going Phase III studies in the US. Licencing is expected in September 2014 for Europe for all genotypes.

In the ELECTRON Phase IIb trial, with Sofosbuvir and Ribavirin, the SVR rates were 84% (21/25) in previously untreated patients, but only 10% (1/10) in treatment-experienced patients after 12 weeks of Sofosbuvir plus Ribavirin. In the SPARE Phase IIb trial in previously untreated patients with unfavourable treatment characteristics (majority of males, IL28B non-CC, high body weight, HCV Genotype 1a and cirrhosis), 68% (17/25) of patients receiving weight-based Ribavirin and 48% (12/25) of those receiving a low fixed dose of Ribavirin achieved an SVR after 24 weeks of therapy. In the QUANTUM study, previously untreated patients infected with Genotype 1 treated for 12 or 24 weeks achieved SVR rates of 47% to 53%. SVR was achieved in 75% of treatment-naïve and –experienced HIV co-infected patients (85/114) in the PHOTON-1 Phase III trial. According to the European recommendations this combination is suboptimal in patients infected with HCV Genotype 1. Licencing was granted in January 2014 for Europe for all Genotypes.

In the COSMOS Phase IIb trial with Sofosbuvir and Simeprevir with and without Ribavirin, 80 prior null-responders with no or mild fibrosis were treated 12 or 24 weeks. The SVR rates were 96% (26/27) and 93% (13/14) for 12 weeks of therapy with and without Ribavirin, respectively, and 79% (19/24) and 93% (14/15) for 24 weeks of therapy with and without Ribavirin, respectively. In 87 previously untreated patients, and prior null responders with moderate fibrosis or cirrhosis SVR rates at week 4 post treatment were 100% (7/7) and 100% (12/12) with and without Ribavirin, respectively, in previously untreated patients, and 100% (7/7) and 93% (14/15) with and without Ribavirin, respectively, in prior null responders. This is still very early data and more information, particularly SVR rates at week 12 will be due shortly. This combination was submitted in the US for licencing in May 2014.

Phase IIb results with the combination of Sofosbuvir and Daclatasvir with and without Ribavirin for 12 weeks and 24 weeks. With 24 weeks, the SVR rates were 100% in previously untreated patients, and 100% (21/21) and 95% (19/21), respectively, in patients who did not respond to dual therapy and triple therapy with Telaprevir or Boceprevir. With 12 weeks of therapy, SVR was achieved in 98% (40/41) of previously untreated patients without Ribavirin (the remaining patient was lost to follow-up).

Based on the above results, the European recommendations at the moment are as follows:



The treatments in orange are not as highly recommended based on clinical evidence.

Genotype 1 - The Future (2015 -2016)

In the SAPPHIRE I study, which is a Phase 3 Interferon free study of 12-weeks, 473 previously untreated patients with Genotype 1 received a regimen of Abbvie's 3 drug combination (ABT450/r, Ombitasvir, Dasabuvir) and weight based Ribavirin. SVR rate was 96.2%. 0.2% of people did not respond to treatment and 1.5% of people relapsed after treatment. SVR rates were comparable among Genotype 1a and 1b patients (95.3% and 98%, respectively). The most common side effects were headache and fatigue. People discontinuing due to side effects were 0.6%.

In the SAPPHIRE II study, which is a Phase 3 interferon free study of 12-weeks, 297 previously treated patients with Genotype 1 received a regimen of Abbvie's 3 drug combination (ABT450/r, Ombitasvir, Dasabuvir) and weight based Ribavirin. SVR rate was 96.3% (286/297). 2.4% of patients had virologic failure. SVR rates in relapsers, partial-responders, and null-responders were 95.3%, 100%, and 95.2%, respectively. SVR rates were comparable among Genotype 1a and 1b patients (96.0% and 96.7%, respectively). The most common side effects were headache and fatigue. People discontinuing due to side effects were 1.0%. It is important to note that in both of these studies, there was a small group on a placebo and they reported similar levels of side effects.

No information is currently available on the TURQUOISE I study, which is a Phase 3 interferon free study for HIV co-infection. This is currently enrolling patients.

In the TURQUOISE II study, which is a Phase 3 Interferon free study 380 patients with Genotype 1 with cirrhosis received a regimen of Abbvie's 3 drug combination (ABT450/r, Ombitasvir, Dasabuvir) and Ribavirin. Patients were randomized to receive the 3 drugs and Ribavirin for either 12 weeks or 24 weeks. In the 12 week group 58.7% of patients had been treated before and in the 24 week group 57% of patients had been treated before. SVR rates were 91.8% and 95.9% in 12 week and 24 weeks group respectively. The difference between treatment arms was not statistically significant. The 3 most common adverse events in Arms A and B were fatigue, headache and nausea. People discontinuing due to side effects were 2.0%.

The PEARL III study is a phase 3 trial to examine a 12 week regimen of a 3 drug combination (ABT450/r, Ombitasvir, Dasabuvir) with and without Ribavirin in people with Genotype 1b. Patients were randomized into a group with Ribavirin and a group without Ribavirin. SVR rates were 99.5% in the group with Ribavirin and 99.0% in the group without Ribavirin. No patients discontinued due to side effects. It was determined that Ribavirin is not needed in these patients.

In the ION-1 Phase 3 study they evaluated the combination of Sofosbuvir and Ledipasvir by Gilead in previously untreated patients with Genotype 1 to determine if Ribavirin (RBV) or longer treatment duration is required to achieve a high SVR rate. 865 patients were split into 4 groups. The first was Sofosbuvir and Ledipasvir for 12 weeks with an SVR rate of 99%. The second was Sofosbuvir and Ledipasvir with Ribavirin for 12 weeks with an SVR of 97%. The third was Sofosbuvir and Ledipasvir for 24 weeks with an SVR of 98% and the last group was Sofosbuvir and Ledipasvir with Ribavirin for 24 weeks with an SVR rate of 99%. Also in this study, 15 -17% of each group had patients who had cirrhosis. SVR rates ranged between 94-100% in patients with cirrhosis. The main side effects were fatigue, headaches and nausea but they were seen more frequently in the groups with Ribavirin than in the other two groups.

The ION-2 phase 3 study examined the combination of Sofosbuvir and Ledipasvir (once daily tablet) in previously treated patients with Genotype 1. Patients were randomized to receive Sofosbuvir/Ledipasvir or Sofosbuvir/Ledipasvir with Ribavirin for 12 or 24 weeks. 440 patients were treated. Patients receiving Sofosbuvir/Ledipasvir with or without Ribavirin achieved an SVR rate of 94-96%. The study also showed that adding Ribavirin to the regimen and/or increasing the length of treatment to 24 weeks did not significantly increase the SVR rates. One treatment experienced patient did not respond to treatment. There were 11 patients who relapsed after treatment, 7 of which had cirrhosis. No patients stopped treatment due to side effects.

In the ION-3, phase 3 study, the combination of Sofosbuvir and Ledipasvir with or without Ribavirin (RBV) in previously untreated non-cirrhotic patients with Genotype 1 was examined for durations of 8 weeks of treatment. 647 Patients were split into three groups. The first was Sofosbuvir and Ledipasvir for 8 weeks which achieved an SVR of 94%, the second Sofosbuvir and Ledipasvir and Ribavirin for 8 weeks with an SVR of 93% and the third group was Sofosbuvir and Ledipasvir for 12 weeks with an SVR of 95%.

No significant difference was seen between the three groups but the 8 week groups had higher relapse rate than the 12 week group. The main side effects were fatigue, headaches and nausea but they were seen more frequently in the group with Ribavirin than in the other two groups.

In a small study, looking at difficult to treat patients, 12 weeks of Sofosbuvir and Ledipasvir was evaluated in 20 patients with Genotype 1 and advanced cirrhosis as well as 19 patients who had failed on prior clinical trials with either Sofosbuvir with Ribavirin and another experimental drug or just 6 weeks of Sofosbuvir, Ledipasvir and Ribavirin. SVR rates 12 weeks after treatment are still pending but 4 weeks after treatment the cirrhotic group had an SVR rate of 89% and the patients who had failed on the other Sofosbuvir containing clinical trials were 100%.

A new experimental drug GS-5816 by Gilead used in combination with Sofosbuvir is also being examined for use in all Genotypes according to a phase 2 trial results presented at EASL. It is Interferon and Ribavirin-free. The company is hoping to produce the Sofosbuvir and GS-5816 combined in a single tablet. This study included 154 previously untreated hepatitis C patients without liver cirrhosis of which 35% had Genotype 1. Patients were assigned to receive Sofosbuvir plus either 25mg or 100mg GS-5816 for 12 weeks. Genotype 1 SVR rates were 96% (26/27) and 100% (28/28), respectively, in the 25mg and 100mg dose groups but the numbers are very small. The patient who did not achieve an SVR relapsed after the end of treatment. The most common side-effects reported by at least 10% of participants were fatigue, headache, nausea and constipation. No one developed anaemia, a side-effect often seen with Ribavirin.

The C-Worthy Study, a phase 2 trial by Merck Sharp & Dohme assessed the combination of MK-5172 and MK-8742 with and without Ribavirin for treatment durations of either 12 weeks or 18 weeks, in patients with hepatitis C Genotype 1. There were 4 main groups assessed. The first is in 94 previously untreated patients without cirrhosis. The second is in 123 previously untreated patients with cirrhosis. The third is in 130 previously treated null responding patients with cirrhosis and without cirrhosis. The final group was HIV/Hep C co-infection with and without cirrhosis. The results showed that overall SVR rates after 4 weeks were between 90-100%. 90-97% of cirrhotic patients achieved an SVR after 4 weeks. 91-100% of prior null responders achieved an SVR after 4 weeks. In previously untreated patients with cirrhosis the combination was very effective regardless of the use of Ribavirin or the extended period of treatment (18 weeks). In the HIV co-infection group 90-97% had an SVR after 4 weeks. Common side effects were fatigue, headache, nausea, dizziness, and insomnia and again more prevalent in the groups taking Ribavirin. This is promising and the Phase 3 trials are planned and will commence in the coming months.

In the Hallmark Phase 3 trial, a combination of Daclatasvir and Asunaprevir in patients with Genotype 1b only. There were three groups examined. The first was treatment for previously untreated patients who achieved an SVR of 90%. The second was for patients who had not responded to prior treatments or who had relapsed after treatment which achieved an SVR of 82%. The third group was for patients who were ineligible or intolerant to pegInterferon for reasons such as depression, anemia, advanced fibrosis or cirrhosis. This group also achieved an SVR rate of 82%. Common side effects were headache, fatigue and nausea.

GENOTYPE 2

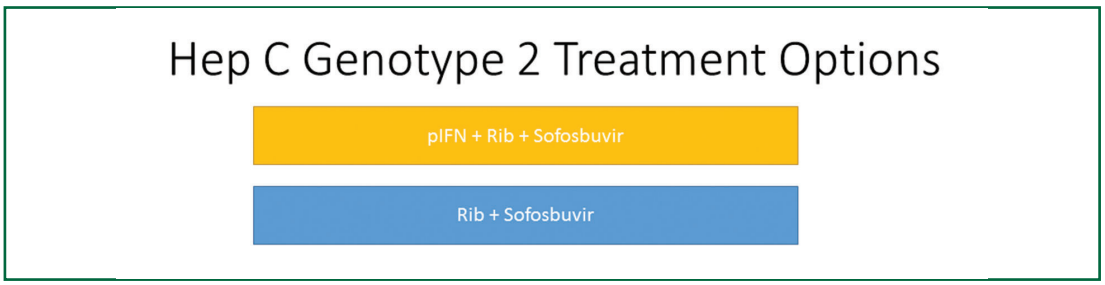
Unlike Genotype 1, there has not been a lot of development in relation to treatments and potential options. This is mainly due to one reason, the relative effectiveness of treatment for Genotype 2 when compared to other genotypes. Using just pegInterferon (pIFN) and Ribavirin (RBV) SVR rates were 70-80% and in some cases only 24 weeks of treatment was required. This is not to say that treatment with the combination of pIFN and RBV is an easy treatment to get through. There are still a significant number of people who either fail on this option for treatment as well as many who treatment with pIFN is not an option due to contra-indications.

Genotype 2 - (2014)
In the FISSION clinical trial, a phase 3 study in previously untreated patients with Genotype 2. 20% of these patients had cirrhosis. In the trial, 137 people with hepatitis C Genotype 2 were randomly assigned to receive Sofosbuvir and Ribavirin for 12 weeks or pegInterferon and Ribavirin for 24 weeks, which resulted in an SVR rate of 97% for the Sofosbuvir-Ribavirin group and 78% the pegInterferon-Ribavirin group. Side effects (including fatigue, headache, nausea, and neutropenia) were less common with Sofosbuvir group than with pegInterferon.

In the FUSION clinical trial, a phase 3 study in previously treated patients with Genotype 2. 28% of these patients had cirrhosis. In the trial, 68 people hepatitis C Genotype 2 were randomly assigned to receive Sofosbuvir and Ribavirin for 12 weeks (36) or Sofosbuvir and Ribavirin for 16 weeks (32), which resulted in an SVR rate of 86% for the 12 weeks of treatment group and 94% in the 16 weeks of treatment group. In both studies, response rates were lower among those with cirrhosis (96% in the 12 week group and 100% in the 16 week group) than among those without cirrhosis (60% in the 12 week group and 78% in the 16 week group. The most common adverse events were headache, fatigue, nausea, and insomnia; the overall rate of discontinuation of Sofosbuvir was low (1 to 2%).

In the LONESTAR-2 trial, 23 patients with Genotype 2 were treated with Sofosbuvir and pIFN and RBV. 60% had cirrhosis. 100% of patients without cirrhosis and 93% of patients with cirrhosis achieved an SVR. Side effects included fatigue, headache, nausea, and neutropenia. The study did not progress to Phase 3 as results from the FISSION and FUSION clinical trials results.

Based on the above results, the European recommendations at the moment are as follows:



The treatments in orange are not as highly recommended based on clinical evidence.

Genotype 2 - The Future (2015 -2016)
A combination therapy of Sofosbuvir (licenced in January 2014) and Daclatasvir (expected to be licenced in September 2014) was examined in patients with Genotype 1, 2, or 3. In this study, patients were randomly assigned to Daclatasvir (once daily tablet) plus Sofosbuvir (once daily tablet), with or without Ribavirin, for 24 weeks. A total of 92% of 26 patients with genotype 2 had an SVR. The most common adverse events were fatigue, headache, and nausea.

A new experimental drug GS-5816 used in combination with Sofosbuvir is also being examined for use in all genotypes according to a phase 2 trial results presented at EASL. It is Interferon and Ribavirin-free. The company is hoping to produce the Sofosbuvir and GS-5816 combined in a single tablet. This study included 154 previously untreated hepatitis C patients without liver cirrhosis of which 14% had Genotype 2. Patients were assigned to receive Sofosbuvir plus either 25mg or 100mg GS-5816 for 12 weeks. Genotype 2 SVR rates were 91% (10/11) and 100% (10/10), respectively, in the 25mg and 100mg dose groups but the numbers are very small. The most common side-effects reported by at least 10% of participants were fatigue, headache, nausea and constipation. No one developed anaemia, a side-effect often seen with Ribavirin.

GENOTYPE 3

Unlike Genotype 1, there has not been a lot of development in relation to treatments and potential options until now. With the new treatments that have been developed and tested, Genotype 3 is starting to be noticed and unfortunately not in a good way. In the past Genotype 3 was associated with Genotype 2 as an easier to treat group. This may have not been the case. Of the people who started treatment a number would either fail on older treatments and there would be many who treatment with pegInterferon is not an option due to contra-indications. With the growing number of people with Genotype 3 being monitored and treated it is becoming clear that not only is it not as easy to treat as previously thought but some people with Genotype 3 may be at an increased risk of mortality, liver cancer and fibrosis progression. With the treatments that are now currently licenced treatment options are much better and the future looks much brighter as well.

Genotype 3 - (2014)

In the FISSION clinical trial, a phase 3 study in previously untreated patients with Genotype 3. 20% of these patients had cirrhosis. In the trial, 359 people with Genotype 3 were randomly assigned to receive Sofosbuvir and Ribavirin for 12 weeks (183) or pegInterferon and Ribavirin for 24 weeks (176). An SVR rate of 56% for the Sofosbuvir and Ribavirin group and 63% the pegInterferon-Ribavirin group. Side effects (including fatigue, headache, nausea, and neutropenia) were less common without pegInterferon.

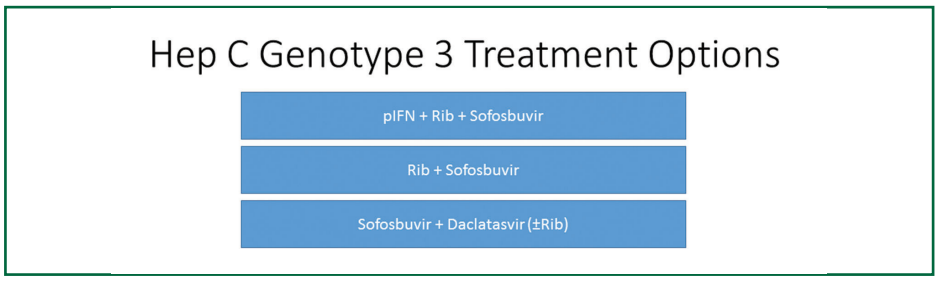
In the FUSION clinical trial, a phase 3 study in previously treated patients with Genotype 3. 39% of these patients had cirrhosis. In the trial, 127 people with Genotype 3 were randomly assigned to receive Sofosbuvir and Ribavirin for 12 weeks (64) or Sofosbuvir and Ribavirin for 16 weeks (63). An SVR rate of 30% for the 12 weeks of treatment group and 62% the 16 weeks of treatment group. In both studies, response rates were lower among those with cirrhosis (37% in the 12 week group and 63% in the 16 week group) than among those without cirrhosis (19% in the 12 week group and 61% in the 16wk group. For patients with Genotype 3, particularly those who have cirrhosis or who have not had a response to prior treatment with interferon, extending the duration of treatment to 16 weeks may provide an additional benefit.The most common side effects were headache, fatigue, nausea, and insomnia; the overall rate of discontinuation of Sofosbuvir was low (1 to 2%).

In the LONESTAR-2 trial, 23 patients with Genotype 3 were treated with Sofosbuvir and pIFN and RBV. 60% had cirrhosis. 83% of patients with and without cirrhosis achieved an SVR. Side effects included fatigue, headache, nausea, and neutropenia.

In the VALENCE study, 328 patients with Genotype 3 infection, were allocated to receive Sofosbuvir and Ribavirin or placebo for 12 weeks. On the basis of data from phase 3 trials FISSION and FUSION suggesting that patients with Genotype 3 had higher response rates when they were treated for 16 weeks, as compared with 12 weeks, the study was extended to 24 weeks. 85% with Genotype 3 infection who were treated for 24 weeks achieved an SVR. Response rates were 80% and 60% among those without and those with cirrhosis, respectively. The most common adverse events were headache, fatigue, and pruritus.

In a study of 28 Genotype 3 patients who were previously untreated, Daclatasvir (once daily tablet) plus Sofosbuvir (once daily tablet) was given, with or without Ribavirin, for 24 weeks. An SVR rate of 100% for the Sofosbuvir and Daclatasvir group and 93% the Sofosbuvir and Daclatasvir and Ribavirin group.

Based on these results these studies, the European recommendations at the moment are as follows:



Genotype 3 - The Future (2015 -2016)
A trial from Gilead with fixed dose combination (one tablet) of Sofosbuvir and Ledipasvir with and without Ribavirin has been carried out on previously untreated patients with Genotype 3. 51 people with hepatitis C Genotype 3 were randomly assigned to receive Sofosbuvir and Ledipasvir (25) or Sofosbuvir and Ledipasvir with Ribavirin (26) for 12 weeks. An SVR rate of 64% for the Sofosbuvir and Ledipasvir group and 100% the Sofosbuvir and Ledipasvir with Ribavirin group. Side effects (including fatigue, headache, nausea, and neutropenia) were less common with Sofosbuvir group than with pegInterferon. Treatment was well tolerated and side effects were more common in the Sofosbuvir and Ledipasvir with Ribavirin group. This combination was submitted for licensing in the US in early May 2014.

A new experimental drug GS-5816 used in combination with Sofosbuvir also by Gilead is also being examined for use in all genotypes according to a phase 2 trial results presented at EASL. It is Interferon and Ribavirin free. The company is hoping to produce the Sofosbuvir and GS-5816 combined in a single tablet. This study included 154 previously untreated hepatitis C patients without liver cirrhosis of which 35% had Genotype 3. Patients were assigned to receive Sofosbuvir plus either 25mg or 100mg GS-5816 for 12 weeks. Genotype 3 SVR12 rates were 93% (25/27) and 93% (25/27), respectively, in the 25mg and 100mg dose groups but the numbers are very small. There was one person who did not respond to treatment and two people relapsed after treatment. There was also one reinfection. The most common side-effects reported by at least 10% of participants were fatigue, headache, nausea and constipation. No one developed anaemia, a side-effect often seen with Ribavirin.

GENOTYPE 4

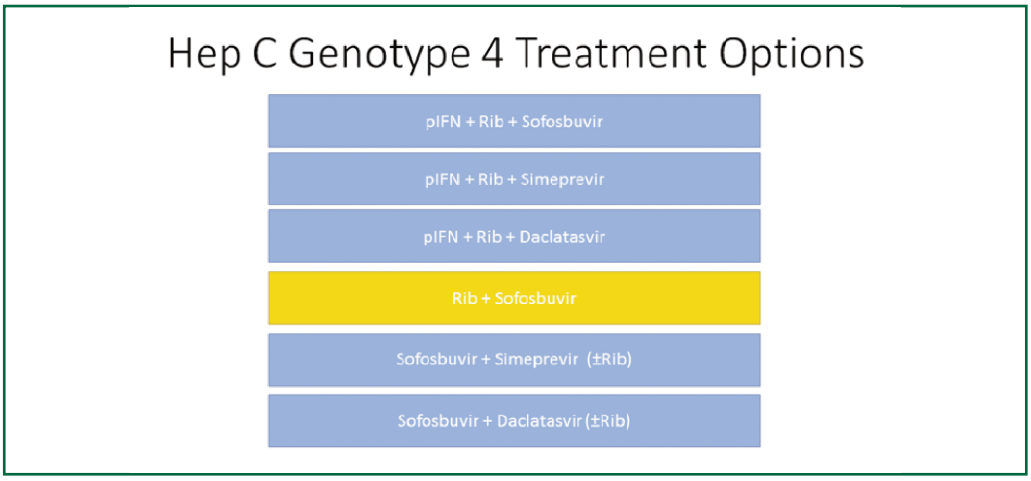
Like Genotype 1, Genotype 4 has traditionally been considered difficult to treat compared to Genotypes 2 and 3. Most direct-acting antiviral agents (DAAs) have only been tested in small numbers of people with Genotype 4 and some have shown minimal activity against this Genotype.

Genotype 4 - (2014)
The NEUTRINO study previously showed that Sofosbuvir (which was licenced in Europe in January 2014) plus pegInterferon (pIFN) and Ribavirin (RBV) produced a cure rate of 96% for the 28 treatment-naive patients with Genotype 4. A phase 2b trial was presented at EASL 2014, which included 60 people with Genotype 4. Just under half had not taken treatment for hepatitis C before (treatment-naive), most of whom were deemed ineligible to use pIFN. The rest had previously been treated with interferon-based therapy, including relapsers, non-responders and those who stopped due to intolerance. Almost one-quarter had liver cirrhosis. All patients completed treatment. SVR rates were 68% in the 12-week treatment group, rising to 93% in the 24-week group. Among the naïve group, the 12 and 24 week SVR rates were 70% and 100%. In those who were treatment-experienced, SVR rates were 59% and 87%, respectively. In treatment-naive patients treated for 12 weeks, people with cirrhosis had a lower SVR rate than people who did not have cirrhosis (33 vs 91%), but responses were similar in the other treatment arms. IL28B non-CC status was also associated with poorer response in the 12-week arms. There were three serious adverse events in the 24-week arm. One person in this group discontinued ribavirin early due to an adverse event and continued on Sofosbuvir monotherapy. The most common side-effects were headache, insomnia and fatigue. No participants developed severe anaemia, though four people (14%) in the 24 week arm had mild anaemia.

In a phase III trial, Simeprevir (Olysio®, licensed in Europe in May 2014) with pIFN / RBV was carried out in 107 people with Genotype 4 who were treatment-naive or treatment-experienced. The treatment consisted of Simeprevir and pIFN/RBV for 12 weeks, followed by pIFN/RBV alone for between 12/36 weeks, depending on the response to treatment. All prior non-responders had to do 36 weeks of pIFN/RBV. 42% of people had not received treatment and 28% of the group had cirrhosis. SVR rates were 65.4% overall. In treatment naïve and relapsers the SVR rates were 83% and 86%, respectively. Partial or null responder SVR rates were lower at 60% and 40%, respectively. In patients with cirrhosis, 46.7% achieved SVR. SVR rates in IL28B CT and TT patients were 65.6% and 59.5%, respectively. Side effects were mainly mild. Serious side effects were uncommon (4.7% of patients) and considered unrelated to Simeprevir. The most common side effects were flu-like symptoms, weakness and fatigue.

In a Phase IIb clinical trial, (COMMAND-1) from 2011, treatment-naïve, Genotype 4 patients were given 12 weeks of treatment with Daclatasvir (expected to be licensed in Europe in September 2014), in combination with pIFN/RBV. Patients were split into two groups with a lower dose and a higher dose of Daclatasvir. SVR was achieved in 58% (7/12) and 100% (12/12) of patients in the lower dose and the higher dose groups, respectively. Serious adverse events occurred in 7.5% of patients and the most commonly reported side effects across all groups were fatigue and headache.

Based on these results these studies, the European recommendations at the moment are as follows:



The treatments in orange are not as highly recommended based on clinical evidence. There is also no information currently on the use of pIFN free treatments in Genotype 4.

Genotype 4 - The Future (2015 -2016)

The Abbvie PEARL-1 study examined ABT-450/r in combination with Ombitasvir, with or without Ribavirin in patients who were previously untreated and treatment-experienced, who did not have cirrhosis. All patients received treatment for twelve weeks. People who had not taken treatment before were split into two groups without (n = 43) or with (n = 42) Ribavirin. The treatment-experienced patients (n = 49) all received Ribavirin. All 42 treatment-naive patients in the Ribavirin-containing group achieved SVR. The SVR rate was 90.9% in group. In those that did not have an SVR, one patient did not return for his SVR blood test, one failed to get a response before treatment finished and two patients relapsed after completing treatment and before week 12 after treatment. All 49 treatment-experienced patients were clear at the end of treatment. Only 37 of these are 4 weeks post treatment and all were clear at this stage as well but SVR results will be required in order to determine if all patients have achieved a cure. No participant in the study stopped treatment due to side-effects and the only serious adverse event occurred as a result of a car accident unrelated to treatment. The most common side-effects were tiredness and headache.

The Ribavirin-free combination of Daclatasvir, Asunaprevir and BMS-791325 combination by Bristol Myers Squibb is also been evaluated in treatment naive patients with Genotype 4 in an expansion of their study (AI443–014). There were two groups receiving different amounts of BMS-791325. All patients completed 12 weeks of therapy. All patients (21) were clear at the end of treatment. SVR rates in the lower dose group were 10/11 patients (one patient missed the SVR blood test at week 12, but was clear 24 weeks after treatment and 9/10 patients in the higher dose group (one patient missed the SVR 12 week blood test). There were no serious side effects and the most frequent were headache (29%), insomnia (19%), nausea (14%), and pain (14%).

A new experimental drug GS-5816 used in combination with Sofosbuvir is also being examined for use in all genotypes according to a phase 2 trial results presented at EASL. It is Interferon and Ribavirin free. The company is hoping to produce the Sofosbuvir and GS-5816 combined in a single tablet. This study included 154 previously untreated hepatitis C patients without liver cirrhosis of which 9% had Genotype 4. Patients were assigned to receive Sofosbuvir plus either 25mg or 100mg GS-5816 for 12 weeks. Genotype 4 SVRrates were 100% (7/7) and 86% (6/7), respectively, in the 25mg and 100mg dose groups but the numbers are very small. The one patient in the second group has not returned for his SVR 12 week blood test. The most common side-effects reported by at least 10% of participants were fatigue, headache, nausea and constipation. No one developed anaemia, a side-effect often seen with Ribavirin.

HIV CO-INFECTION

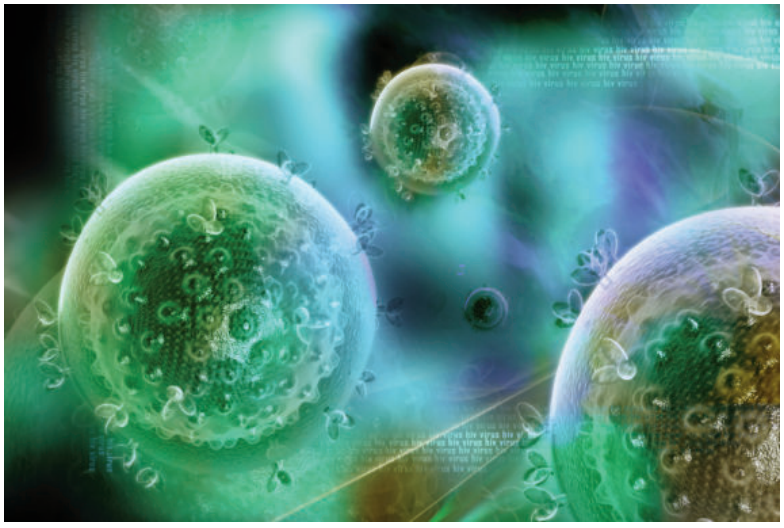
"The indications are the same in hepatitis C mono-infected and HIV co-infected patients." This is a direct quote from the recently published European guidelines on treatment. Whilst HIV needs to be considered for additional complications such as faster progression of disease and potential antiretroviral therapy (ART) drug interactions, there is no difference in the results of achieving an SVR in the two groups. In order to see what treatments are coming in the near future please refer to the specific article on your Genotype.

In relation to the HIV and drug interactions between the new hepatitis C drugs that should be licenced in Europe by the end of 2014 and antiretroviral's for HIV, some changes may be required to current HIV medications. For Sofosbuvir containing regimens, which is a once daily tablet and licenced in January 2014, no interactions are expected for the majority of ART. For Simeprevir containing regimens, a once a day tablet which was licenced in May 2014, there are some contra-indications for people on certain antiretroviral drugs. These include Cobicistat-based regimens, Efavirenz, Delavirdine, Etravirine, Nevirapine, Ritonavir, and any HIV Protease Inhibitor, boosted or not by Ritonavir. For Daclatasvir containing regimens, a once daily tablet which is expected to be licenced in September 2014, and a dose change will be required in the Daclatasvir for patients receiving Atazanavir/Ritonavir and Efavirenz but a change of antiretrovirals may not be required.

At the EASL Conference in London there was information on two trials that are currently taking place. In a RBV-free regimen of Sofosbuvir and Ledipasvir on 50 patients with Genotype 1, treatment naïve, and with stable HIV disease, received a once daily tablet of the combination of Sofosbuvir and Ledipasvir for 12 weeks in two different groups.

Group A were antiretroviral therapy (ART)-naive, HIV long-term non-progressors and Group B were patients on permitted ART therparies with HIV suppression. In ART naive patients who have completed treatment (8), the SVR after 4 weeks is 100%. In ART treated patients, 100% achieved viral suppression by 4 weeks with continued viral suppression. There were 2 cases of mild anaemia, no serious adverse events or discontinuations due to side effects. In HIV/HCV co-infected patients, a 12-week regimen of Sofosbuvir and Ledispasvir elicited rapid and complete hepatitis C suppression on treatment, mirrored rates observed in hepatitis C mono-infected patients. In a Phase II trial (C-Worthy) Genotype 1, treatment-naive, non-cirrhotic patients, co-infected with HIV and on a stable anti-retroviral regimen were randomized to a 12-week treatment regimen of MK-5172 and MK-8742 with and without a weight based dose of RBV. 56 out of 59 achieved an SVR after 4 weeks. The SVR after 4 weeks rate with Ribavirin is 97% and without Ribavirin was 90%.

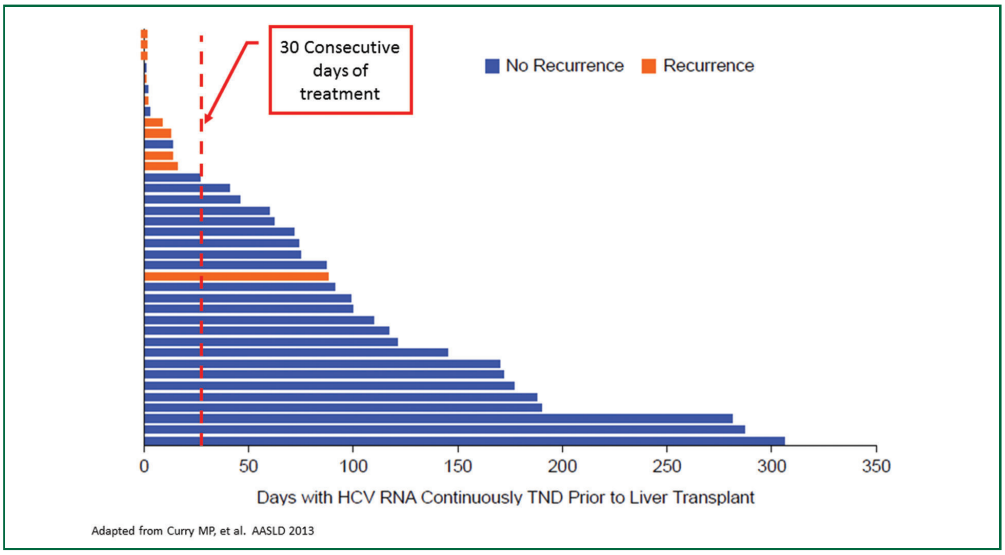
There was no discontinuation due to adverse events and there was no negative effect on HIV suppression. The most common adverse events were: fatigue 10%, headache 5%, back pain 5% and weakness 5%. Oral regimes for co-infection are just as effective as in mono-infection.



PRE LIVER TRANSPLANT

Until the last few years, patients who had advanced cirrhosis or had been indicated for a liver transplant were generally ineligible for treatments. This was for a good reason as in almost all clinical trials with pegInteferon and/or Ribavirin, the side effects are generally more prevalent and have a greater magnitude in patients with cirrhosis compared to those with no, mild or moderate fibrosis. With a number of new drugs being licenced and in the pipeline in the near future, the toxicity of the treatments is significantly less and the possibility to treat patients to prevent decompensation or achieve an SVR prior to liver transplant, to improve the chance of the transplant working, are a very real option.

An initial study of the use of Sofosbuvir and Ribavirin for up to 48 weeks stopping on the day of transplant has been presented. Forty-four patients infected with hepatitis C Genotypes 1 to 4 with liver cancer were treated. In 93%, the virus could not be detected at the time of transplantation. Among them, 64% had achieved an SVR 12 weeks after transplantation. The length of time the virus could not be detected pre-transplant was the best predictor of response. As the graph shows, if the individual receives a minimum of 30 continuous days of treatment prior to transplant the likelihood of reinfection of the new liver is significantly decreased. Although there is no information generated with other drug combinations, it is likely that adding a another drug or a different set of drugs, with or without Ribavirin, will yield more efficient prevention of hepatitis C re-infection of the new liver after transplant. Whether patients with decompensated cirrhosis awaiting liver transplantation should be treated with the same regimens remains is unclear at the moment.



POST LIVER TRANSPLANT

In most people post-transplant, as a result of hepatitis C, the disease returns in approximately 4-12 weeks. In approximately 30% of these, the virus will come back rapidly with significant fibrosis within one year after transplant. These patients are at a higher risk of liver transplant rejection and survival rates fall significantly once cirrhosis has developed.

With Boceprevir and Telaprevir regimens, there are a number of concerns around the safety and tolerability of these treatments in post-transplant patients. Studies have shown that the rate of anaemia is extremely high and 50-90% of these cases require, either a reduction in the amount of Ribaviran (RBV), epo injections (to boost red blood cells) or blood transfusions. Considering this and other adverse events into account such as infections (≈20%), kidney problems (13-40%), and liver rejection (4-6%) there is a high rate of people needing to stop treatment early (25-56%). In an update on one study (REPLACE) using Telaprevir in 52 post-transplant patients with moderate Fibrosis (F0-F3), 67% had no virus 12 weeks after treatment (SVR12). 11% of patients had serious side effects and the most common side effects were anaemia (60%), pruritus (46%), rash (39%), and weakness (37%). Immunosuppression medication was adjusted during treatment and was reported as manageable but required close monitoring. The reality however is that with the increased likelihood of severe side effects, relatively high numbers stopping treatment and with drug interactions in relation to

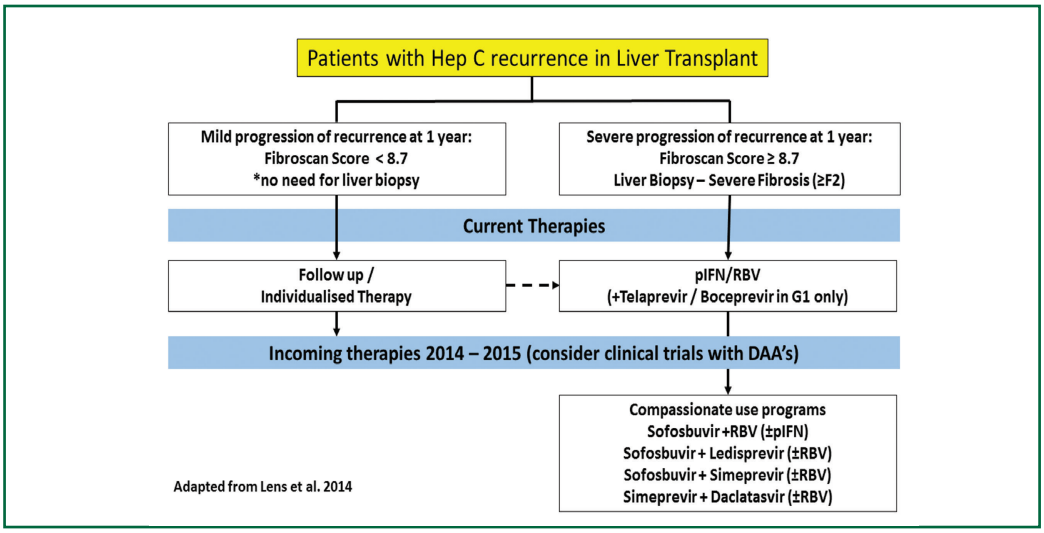
immunosuppression medications, it is unlikely that Telaprevir or Boceprevir will be used in this group of patients due to the fact they require pIFN.

As of January 2014, Sofosbuvir has been licenced in Europe and data from a prospective studies and early access compassionate use programme was presented at the EASL Conference, in April. In the prospective study, Sofosbuvir and RBV were used in 40 naive and treatment experienced patients, all Genotypes, varying stages of fibrosis/cirrhosis, and ≥6 months post-transplantation. The regimen consisted of one tablet of Sofosbuvir and starting with a low dose of RBV and increasing it based on side effects of treatment for 24 weeks. Results 4 weeks after treatment finished (SVR4) were 27/35 (77%) and 4 more patients are currently finished treatment but not yet at SVR after 4 weeks. There were no deaths, graft losses, or drug-drug interactions reported between Sofosbuvir and immunosuppressive medications. Side effects were reported in 52% of people and the most common adverse events were fatigue, headache, arthralgia, and diarrhoea.

In the compassionate use programme, patients who had exhausted all treatment options and had poor clinical prognoses were granted access to Sofosbuvir. The regimens included one tablet of Sofosbuvir a day and RBV for up to 48 weeks, with pegInteferon (pIFN) added if the doctor thought it was appropriate. In 104 patients, preliminary SVR12 rates were 62% for patients. Based on the fact that in many cases, this treatment was there last chance, 62% have improved on treatment, 21% have stabilised and 21% died, with all deaths attributed to progression of liver disease or associated complications. 48% of patients reported side effects, and of 13% of patients reported serious adverse events that results in stopping treatment.

In a phase II study, 34 post liver transplant patients received a 3 drug combination (ABT-450/r, Ombitasvir, Dasabuvir) and Ribavirin for 24 weeks. The patients were Genotype 1, 12 months post liver transplant, and had moderate fibrosis (≤F2). There are currently 26 patients that have reached 12 weeks post treatment. 96.2% have achieved an SVR. One individual relapsed 3 days after treatment. In relation to side effects, headache (44%) and fatigue (41%) were the most common. The only consideration when using this combination was the interaction between the 3-drug combination and the use of immunosuppression medication. When on this regimen, immunosuppression medication was adjusted as the half-life of the immunosuppression medication was extended by between 3-7 times. There are also 2 other clinical trials being carried out. The first is with Daclatasvir and Simeprevir and RBV. This is for 24 weeks of treatment in Genotype 1b patients with low to moderate fibrosis (≤F3). The second is with Sofosbuvir and Ledipasvir and RBV. The treatment will be between 12-24 weeks and in Genotypes 1 and 4. All stages of fibrosis are eligible.

In an article by Lens et al, a model was proposed for dealing with patients post liver transplant in the interim while new DAA's are being licensed and assessed for reimbursement.



Finally, there is not a lot of information available about the long-term outcomes of people with hepatitis C after liver transplant and diagnosed with mild fibrosis 1 year after transplantation. A review took place in Spain of 174 patients who underwent a liver transplant between 1999 and 2012 and were diagnosed with mild hepatitis C 1 year after liver transplant. They were monitored for between 3-9 years and the information suggests that most patients in this category have excellent long-term outcomes. Nevertheless, one third of these patients may develop cirrhosis overtime.

ARE INTERFERON & RIBAVIRIN GONE FROM TREATMENT FOR HEPATITIS C?

PegInterferon (pIFN) and Ribavirin (RBV) have been the only options for hepatitis C treatment since 1998 for all Genotypes. Since 2011, the first licenced DAA's (Telaprevir, Boceprevir, Sofosbuvir, Simeprevir) have added pIFN/RBV to increase cure rates as using single DAA's on their own were not sufficient. With pIFN there are significant side effects and in some cases these side effects can be irreversible. Ribavirin also has a significant side effect, most common being fatigue, insomnia, anaemia and irritability. Overall, up to 80% of people on treatment have side effects during treatment and many have to stop treatment as a result. There are several people for whom pIFN/RBV are contra-indicated such as depression, epilepsy, and severe co-morbidities. In January 2014 in Europe, we saw the first product (Sofosbuvir) obtain a licence for Genotype 2 only, which did not need pIFN and with combining DAA's, by the end of 2014 there should be access in Europe to regimens that do not require pIFN and potentially Ribavirin, so are they gone for good?

At the EASL conference in London, the belief was that pIFN would only be used for another 12-18 months, and RBV for a little longer, for the treatment of the majority of people with hepatitis C, although they may not be gone for all. There are some cases that are difficult to treat, particularly some people who have Genotype 3 and have been treated unsuccessfully before. Although there are bad side effects it does have some advantages. In these cases, pIFN and RBV can improve the chance of an SVR and/or reduce the length of the treatment. Also in the future, with those that may need pIFN the side effects may be not as bad. A new liver specific pIFN (pegInterferon-λ) is being developed and shows significantly less side effects than the current pIFN.

A 'MIX & MATCH' APPROACH TO NEW HEPATITIS C DRUGS

The European Association for the Study of the Liver (EASL) has issued new guidelines for the treatment of hepatitis C which recommend that wherever possible, patients should be treated with the newest direct-acting antivirals (DAA's). EASL is also encouraging European physicians to combine products from different pharmaceutical companies to achieve the most potent interferon-free regimens, in its new hepatitis C treatment guidelines presented at the International Liver Congress in London recently.

These guidelines were "designed to accommodate the diversity of European populations and reimbursement practices" The EASL guidelines are another sign that when making prescribing decisions for people with hepatitis C, physicians do not intend to be constrained by licensing indications or the quest of pharmaceutical companies to deliver 'exclusive' drug combinations that require prescribers to use co-formulated (all in one tablet) DAA's from one company.

The guidelines make recommendations for all Genotypes, and include all DAA's that are expected to be licensed in Europe during 2014, including Daclatasvir. Simeprevir received marketing approval in May 2014 and Daclatasvir is expected to be licenced in September 2014. Bristol-Myers Squibb, the developer of Daclatasvir, has anticipated the European move towards a `mix-and-match` approach by applying for a license for Daclatasvir alone in Europe. The guidelines recommend that the first-generation Protease Inhibitors Telaprevir or Boceprevir should be used for treatment of Genotype 1 infection only when newer options are not available. For other Genotypes, the combination of pegylated interferon and ribavirin is described as 'acceptable' where newer options are not available. The guidelines also reference the prioritisation of treatment. All previously untreated and treated patients with compensated disease due to hepatitis C should be considered for treatment. Treatment should be prioritised for patients with significant fibrosis. Treatment is justified in patients with moderate fibrosis and in patients no or mild fibrosis the indication for and the timing of treatment can be individualised.

The guidelines have been printed online as the pace of change in the hepatitis C treatment area is so fast and will updated as soon as approval dates for new Interferon-free combinations are known. These are likely to be approved in late 2014 or early 2015. The full guidelines can be downloaded from the EASL website.

HEPATITIS C - THE COST OF SUCCESS

As discussed in other articles in this magazine, there are several all-oral DAA treatments with SVR rates in the range of 90% or higher and hence there are likely to be several options for therapy of hepatitis C within the 12-18 months. The availability of these new regimens of therapy for hepatitis C will lead to major changes in the management of the disease.

Until now treatment has been based on pegInterferon (pIFN) and was limited by the common and sometimes serious side effects with SVR rates of 70-80% in Genotypes 2 and 3 and 50% or less in Genotype 1 and 4. In patients with certain coexisting conditions interferon was usually contraindicated due to a high rate of side effects and even then was often not effective. In real-life situations, fewer than half of people with hepatitis C qualify for pIFN therapy or decline treatment due to duration and side effects. It also requires significant monitoring from hepatologists, nurses and other health care professionals. With the new regimens, the limitations and medical barriers to treatment, however, may now largely disappear. The ease of administration, short length of treatment, and minimal side effects will probably mean that the vast majority will qualify for treatment. However, not all barriers to treatment will be lifted. The major limitation remaining will be economic.

The current cost of a 12-week regimen of Sofosbuvir alone in the USA is $84,000, or $1,000 per tablet. In France, Sofosbuvir is approximately €67,000 and €60,000 in Germany. A 12-week course of Simeprevir, another new drug in the USA is $66,400. As many of these new regimens will require the combination of two or more drugs like these a course of treatment in the future could be expensive. These new treatments are a somewhat breath taking price, or are they?

Since, pIFN and in some case the RBV is removed, there are significantly less side effects and the treatment length is between half and quarter of the length of time, so these new treatments result in:

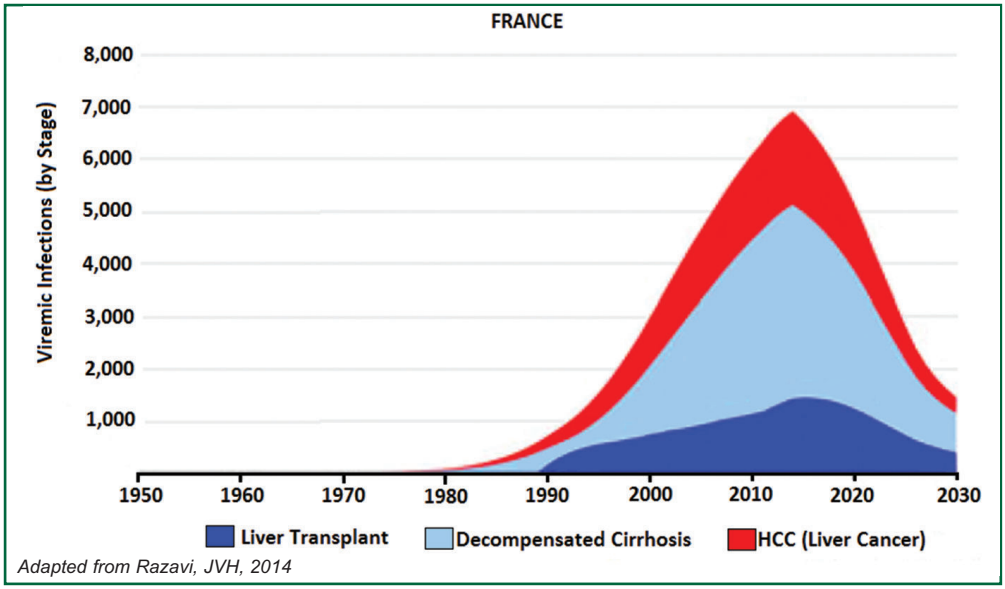
- less need for side effect medications,
- less requirement for hospitalizations,
- less hospital visits, etc.

With all of this in mind, the median cost in the USA of a course treatment for Telaprevir or Boceprevir is approximately $84,000. However, Telaprevir and Boceprevir achieve an SVR rate of 70-80%. So considering the patients that fail treatment and the additional monitoring and side effects they have, this results in a cost per SVR of approximately $195,000. The new regimens are producing SVR rates in excess of 90%. The cost per SVR will be much closer to the cost per treatment. Finally, when you consider that due to the toxicity of pIFN containing treatments, only some people with hepatitis C could be treated with the current regimens. Many of those with late stage cirrhosis, or re, or post liver-transplant were deemed high risk and were not treated and hence progressed to liver transplant which can cost $250,000 - $500,000.

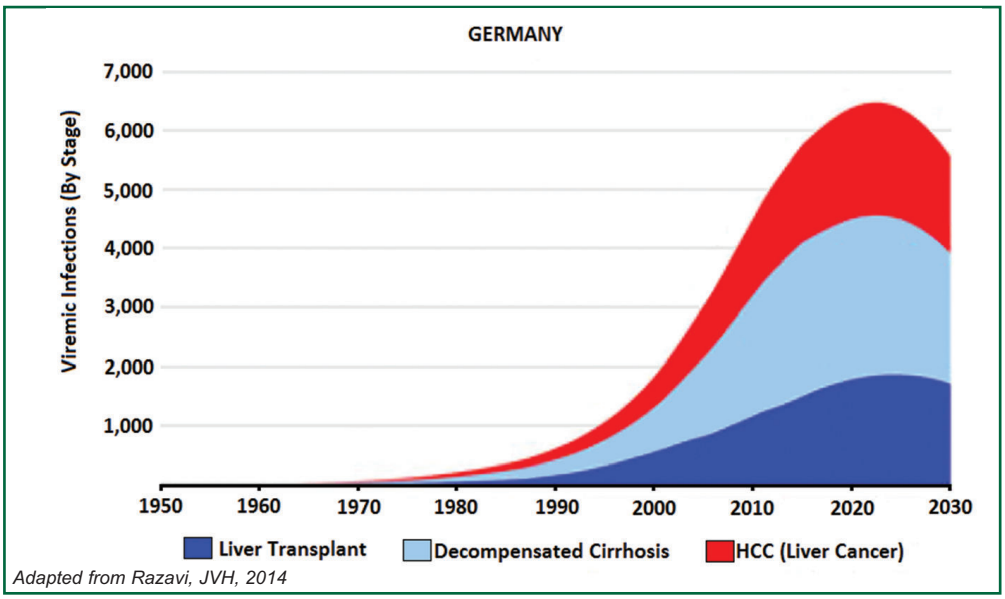
Since the new treatments are significantly less toxic, these patients can be treated, reducing or eliminating this cost in many cases. Overall, whilst still unreasonable prices, they are somewhat justifiable looking solely at costs on individual bases.

Of course with higher prices and a limited budget less people will be treated so on a national and international level, treating hepatitis C will be a significant amount to overburden medical care systems, or will it?

There are several things that need to be considered. The first is the amount of people you treat in a country. In France, between 5-7% of the hepatitis C population are treated annually and 4-5% in Germany. Whilst these are still very low levels of treatment rates, models predict even at these rates the levels of liver transplant, decompensated cirrhosis and liver cancer (HCC) will decrease in France between the years 2015-2020 and in Germany between the years 2020-2025. Whilst many other European countries by 2030 will still continue to see a rise in all these areas, as well as the costs associated with them.



Adapted from Razavi, JVH, 2014



Adapted from Razavi, JVH, 2014

The second thing to consider is by the end of 2015 there should be around 9 new drugs available with at least 5 combinations of drugs made by 5 companies for the treatment of hepatitis C. With SVR rates greater than 90% in almost all categories of people with hepatitis C in these combinations the competition for market share should be significant forcing prices down which ultimately will lead to more people being treated. Sofosbuvir, which could be the backbone for some of these combinations and at a price of $84,000 for a course of treatment, the drug alone could come under fire as negotiations are currently being held by the manufacture to sell in India and Egypt for $2,000-$2,500 and $900, respectively. This could lead to push back by a number of governments and payers in developed countries to reduce the price. Other issues may be re-imports of drugs from these regions or health-tourism to these areas for treatment. From a European perspective, if there are significant differences in the prices for these new drugs within EU countries there may be the potential under the joint procurement directive of a European tender to purchase them on an EU tender basis which could also significantly reduce the price. However, this would be voluntary by each country.

It is also important to remember that these drugs do work extremely well when they are taken correctly. In real life situations, ensuring that the treatments are adhered is extremely important. Ireland is very well placed to do this effectively. A registry (ICORN) for clinical guidelines and the use of these drugs has been created to monitor the use of new drugs.

There is also a significant role for organisations like the IHS to play a part to educate members on preparing for these treatments, not just from a cost perspective but to ensure that each member has the best chance of succeeding and achieving an SVR.

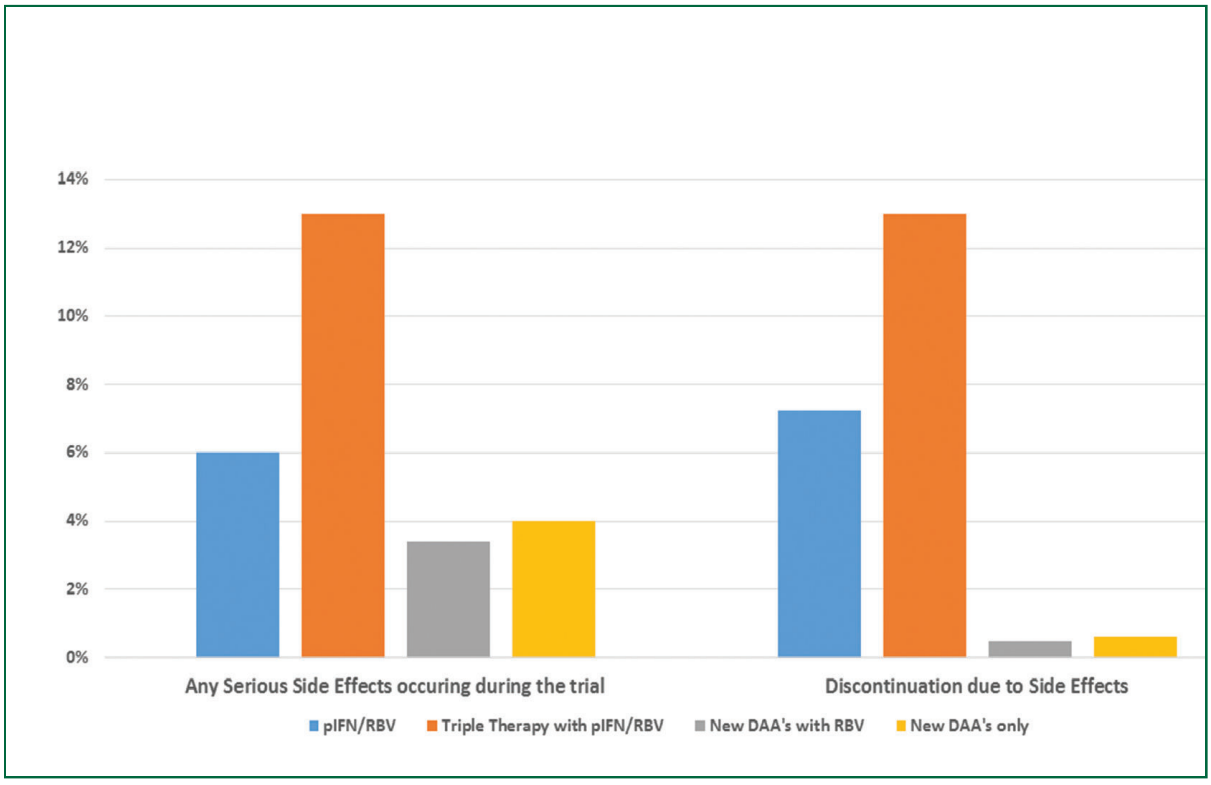
Finally, these new drugs are expensive currently but even at these price levels it still makes sense to provide access to those in need of treatment as soon as possible. With increased competition the prices will come down and hopefully lead to increased access in the long term which will eradicate the virus.

SIDE EFFECTS - WHAT'S THE FUTURE?

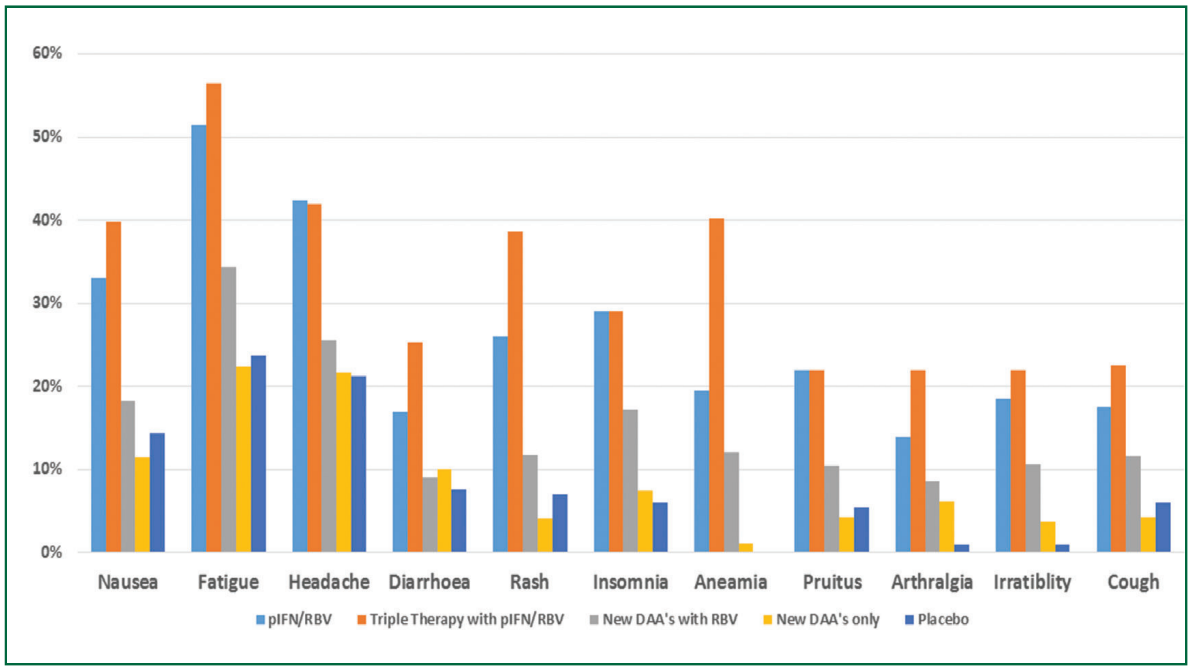
Without a doubt the biggest single impediment in accessing treatment on an individual level is the side effects of treatment. If there were no side effects, even with results as low as 40% with the old dual therapy (PegInterferon and Ribavirin), 6 months or a year of treatment would be relatively easy and worth the risk. People would not have to look closely at how they will take time out of their lives to complete the treatment, how to change their lifestyle or how to stop or reduce work. However, the side effects are a significant part of dual or triple therapy. With the advent of the new therapies this article will examine some of the more common side effects and see are these new treatments really giving significantly less side effects.

The first step is the removal of the pegInterferon (pIFN). Some of the most common side effects associated with this include headache, fatigue, insomnia, nausea, vomiting and skin rash. In 2014 and 2015 it will be possible to remove pIFN from the treatment, increase the SVR rate and reduce a significant amount of these side effects.

The graph below shows a summary of serious side effects reported in the clinical trials for the different types of treatments. It is easy to see that both the serious side effects reported and those severe enough to require the discontinuation of treatment are less with the new treatments with or without Ribavirin compared to dual therapy with pIFN and Ribavirin or triple therapy with either Boceprevir or Telaprevir.



The next step then is the removal of Ribavirin which also has significant side effects. From the graph, below you can see the breakdown of some of the most common side effects and how the removal of the Ribavirin will reduce the side effects even further. However, this may be a little further away, maybe 2015 to 2016 but it is coming close. Finally, if we take a look at just the new DAA's on their own, it still looks like there are some side effects. However, if we take a closer look and compare the DAA's on their own to the placebo groups, it is clear that overall the difference in the amount of side effects between being on the DAA's and being on a placebo is minimal.



SUSTAINED VIROLOGICAL RESPONSE (SVR) IS IT A CURE?

The ultimate goal of hepatitis C treatment is to eradicate hepatitis C infection and reduce the risk of progression of hepatitis C liver complications, including liver failure, cancer, and death but is an SVR a cure? An SVR is when hepatitis C RNA cannot be detected 24 weeks after therapy is completed. In studies the chance of relapse after 24 weeks is extremely low (<1%). There has been a general apprehension about calling an SVR a cure for several reasons. We have seen family members and friends relapse after the end of treatment and before the 24 week mark. We have heard about the very few who reverted after the 24 weeks. We may have also heard about some people who got an SVR and still developed liver cancer or died from liver related issues. To put this in perspective, if you get hit by a car and then manage to blow up the car before it hits you again, there is still the damage from the initial hit to be dealt with. Finally, there may also be a component of self-preservation in their as well. If there is a potential it might come back you can be prepared for that. If it's a cure and it comes back that is a much more difficult thing to deal with as a cure should mean it is gone.

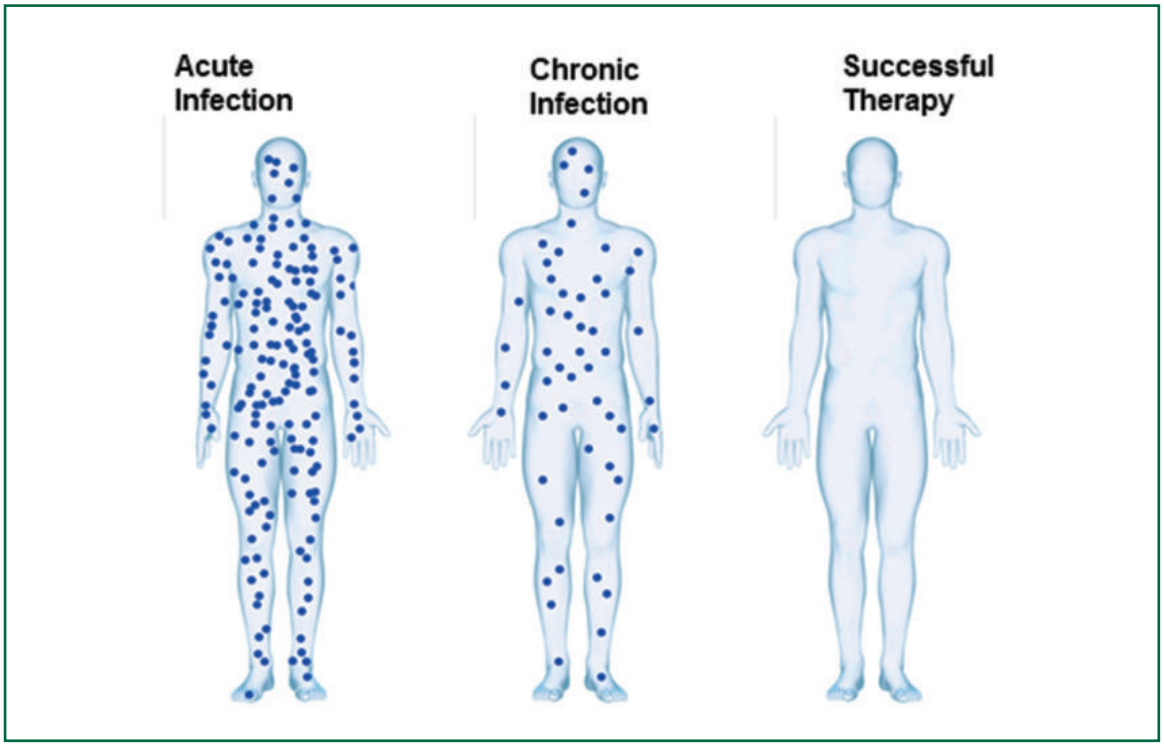
So let's look at the facts. The vast majority of patients who get an SVR have shown improvements on biopsies after treatment compared to before treatment. Both fibrosis stage and amount of inflammation of the liver usually regress. In fact, some authors have reported complete resolution of fibrosis or inflammation after SVR. Several studies have shown that regression of hepatitis C related cirrhosis is possible after an SVR. The scientific reason for this is due to biology of the liver and its ability to heal itself. In an analysis of over 5000 SVR-achieving patients, compared to patients with advanced fibrosis who failed therapy, SVR-achieving patients had a much lower risk of liver decompensation. In another analysis of 286 persons with SVR, the decompensation rate after 5 years was 1% compared to 18%–25% in cirrhotic patients. Furthermore, in an European analysis, 5-year survival among patients achieving SVR was comparable to that of the general population.

So what about the day to day aspects? A study examining quality of life shifts in people cured of hepatitis C, published in 2007, found that those who achieved an SVR saw significant improvement in their general health, sense of vitality, sexual functioning, ability to conduct tasks that require physical strength and stamina, and capacity to fulfill roles that require emotional effort and support, be that within a family setting, with friends or with other intimate acquaintances.

More recently, a study was carried out to evaluate the changes in fatigue in patients receiving the new Sofosbuvir based treatments during some of their clinical trials. After achieving an SVR, patients reported significant improvement relating to fatigue compared to the individuals' own starting point before treatment.

Based on this information, an SVR is a cure. The bottom line is you can call it whatever you want, the treatment works and the rewards that come along with that include a greatly improved outlook in terms of liver function, life expectancy and quality of life.

However, being cured or achieving an SVR doesn't mean cutting all ties with a health care support system. Those who achieve an SVR and who only ever had early stage liver disease may be able to stop seeing the hepatologist and just have their haemophilia centre monitor their virus levels. But those who have cirrhosis should still be monitored by the hepatologist, which means lifelong follow-up no less frequently than once a year. Also, because it is difficult to determine the degree of liver damage after an SVR, it is advised that people who have been cured of hepatitis C should still abstain from alcohol.



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