Positive News

Information Magazine for people with Hepatitis C and HIV

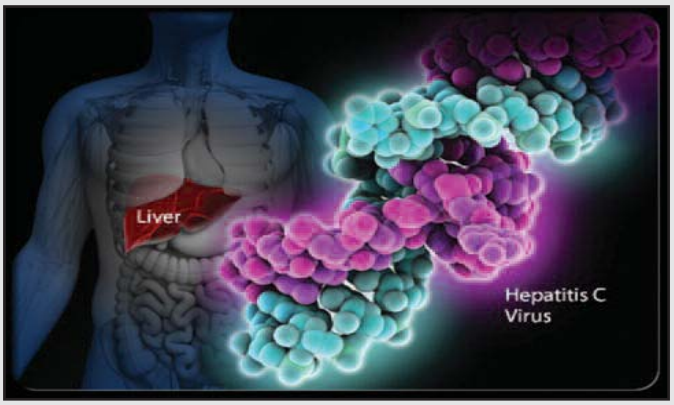
The Irish Haemophilia Society

Representing people in Ireland with haemophilia and related bleeding disorders

Welcome to the December 2015 edition of *'Positive News'*. The edition looks at:

- Patient experiences and perspectives with new Hepatitis C treatments.
- An update from the AASLD Liver Meeting, in November 2015.
- Difficult to treat groups of people.
- Ribavirin and its role in new Hepatitis C treatments.
- A Global review.

New generations of Direct Acting Antivirals (DAA's) are now licensed and being used in Ireland. The success rate with these new therapies are excellent, with minimal side effects and a short duration of treatment. The patient experiences and perspectives in this magazine, may give you a better understanding of the frustrations, realities and doubts around the new treatments, particularly when compared to the older Interferon based treatments.



We hope you enjoy reading this magazine. If you have any queries on any of the articles or any questions about treatment, please contact the Society on 01 6579900. If you are on treatment and need support, the Society can help you. We are offering support and assistance to members currently on or awaiting to go on treatment.

SUPPORTS AVAILABLE FROM THE SOCIETY

If there is anything that the Society can help you with, please call the office on 01 6579900. We are committed to offering practical support and assistance to members on Hepatitis C treatment. We are here to help and to listen. Some of the supports available include the accommodation facility at Hyde Square which is 200 metres away from St. James's Hospital, financial assistance for those travelling long distance to Dublin to have their treatment monitored and reviewed, and personal support during your course of treatment.

Edition: December 2015

In the past year, we have seen the introduction of new treatments for Hepatitis C. In many countries as well as in Ireland, the initial rollout has been restricted to those with cirrhosis until now. Over the last year, there have been many questions from those being offered treatment, those on treatment and those awaiting to go on treatment.

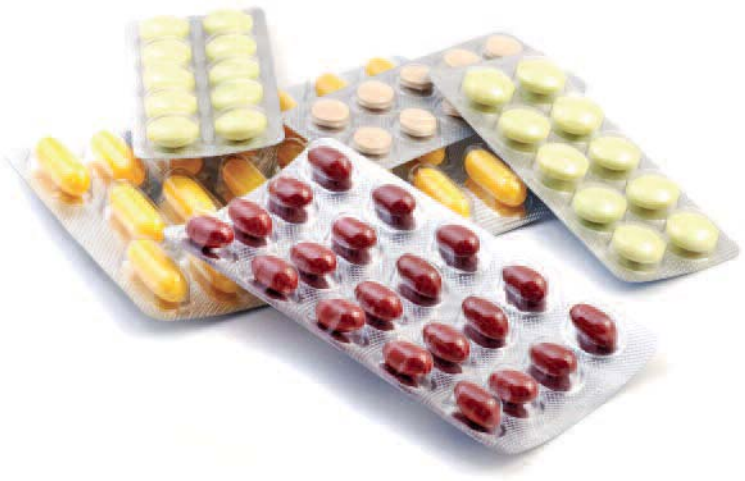
From those who were offered treatment, the majority of the questions have been about the side effects and if the treatments work. In the past, the side effects were significant and some of them lasted not just for the time of the treatment but lingered for weeks or months afterwards. This made treatment difficult to get through. Adding to that the low sustained viral response (SVR) / cure rates meant there were many who did not get through the course of treatment. There was also the feeling that the side effects were minimised before treatment started. Over time, this has improved, but many of the discussions over the last year have been on this topic. Based on past experiences, for some it is difficult to believe that there are almost no side effects. This is based on perspective. In comparison to the side effects of the old treatment of Peg-Interferon/Ribavirin, with the new Direct Acting Antivirals (DAA's) treatments, the side effects are minimal. The likelihood of success is much better (40% to >90%), so it makes the very minimal side effects that occur even easier to deal with. As one person described to me and I thought it was appropriate for the time of year, the difference as *"it's like comparing starting your Christmas shopping on 24th of December and shopping mid-week in the middle of the year."* I needed some clarification on what that meant, and the response I got was very logical. They said, *"On Christmas Eve, the likelihood of success is limited, it's a nightmare, no parking, the shops are crazy, you can't breathe and it's a struggle. So if that's all you knew why would you do it again. On the other hand, midweek in the middle of the year the likelihood of getting shopping done is better, it's planned better, it's usually quicker and there may be a few people that are annoying but its nothing in comparison."* The other version that was explained to me was *"it's like comparing the feeling of getting hit by a bus and getting a slap".* You can choose which one you prefer based on your own perspective, but the simple fact is that they are much shorter in duration with better success and significantly less side-effects.

We have also had comments from some people who are on treatment, (who had been on the last treatment with Peg-Interferon / Ribavirin) saying *"this new treatment is not working because I don't feel anything"* and then four or six weeks into treatment the virus was gone and getting to the end of treatment was even easier. The majority of the discussions on these new treatments have not been around side-effects or duration, they have been around watching the virus disappear. There is usually a large initial drop in the viral load and then it lingers, as the medications hunt out the last few remaining viruses. With those that have finished and are clear, there is a variety of emotions: joy, relief, happiness, confusion and even loss, but all are very happy and they would go through it again.

I would like to take a second to acknowledge the very small percentage (<5%) of people for whom this current combination has not worked. In the last two years, between clinical trials and the early access programme for those with cirrhosis there have been a few people. For those people, who it has not worked for, there were very specific situations and other issues that may have led to failure. The consolation is that the next generation of treatments are even more effective for "difficult-to-treat" people and hopefully for those people who have not been successful, they will have the motivation and determination to go again.

There is a building anticipation from those who are currently awaiting treatment. Now that these new treatments are on the market for over a year and have such a high success rate with side effects and duration of treatment being minimal, those that have been waiting to start, want to close that chapter in their lives and the move on.

In the next few pages, people have kindly talked about their stories and covered some of the topics mentioned in this article, from their own point of view. By reading these, hopefully you will get an idea of other peoples experiences and what they considered when going on treatment. If you have any queries, please don't hesitate to contact the I.H.S., or more importantly contact your specialist and have that conversation.



I was probably exposed to Hepatitis C in the 1970's following treatment for a haemophilia related bleeding episode. I was diagnosed with non A - non B Hepatitis in 1992. This was subsequently defined as Hepatitis C. I was offered Interferon based treatment in the 1990's, but I declined the treatment as I wasn't happy with Interferon and it's possible side effects. My liver status was assessed annually with blood tests and a Fibroscan, when it became available and I was regularly monitored. I also decided not to avail of treatment offered 3 years ago, as I felt optimistic that there would be better options available in the near future. But I was also fearful that treatment wouldn't work or that the treatment might destabilise some other medications that are prescribed for me.

The physical and psychological impacts of Hepatitis C can be severe. When the new generation of medications for Hepatitis C became available this year, subject to meeting certain criteria I was very optimistic that these new treatments are an excellent opportunity for an SVR. They are a *"game changer"* and the timing is right for me. I started the treatment 11 weeks ago and my blood updates indicate significant changes of a very positive nature. My Haemoglobin Hb readings dropped significantly on Ribavirin treatment and I consequently became very fatigued at times. I also had itching in my legs especially at night. I used Ice Gel which seemed to cool inflamed areas. And my GP has prescribed a cream which seems to calm the itch.

"I started the treatment 11 weeks ago and my blood updates indicate significant changes of a very positive nature."

I've attended appointments to verify my weekly status. At week 8 the virus was undetectable.

This is fantastic news. I was very optimistic starting out with this treatment as I felt that this treatment was right for me. It's extraordinary to think that a very significant health issue that I've had for over 30 years has now been dealt with in a very positive manner. The medical team looking after me have been exemplary in their care and attention. I would encourage any person considering these new treatments to discuss it with their consultant or medical team and to go on the treatment if deemed suitable.

These new treatments herald a bright future for patients with Hepatitis C. This treatment works!

Waiting for treatment is a pain. It doesn't matter if it's life-threatening or not, the simple act of waiting is difficult. We live in a McCulture that tells you if it's available then you should have it NOW NOW NOW! Patience be damned! Procedure? Throw it out the window! You are entitled to it and so it should be yours. With this pervasive attitude, it can be draining to wait. When your specialist tells you that a new treatment should be available in a few years, and then says that every time you visit for a "few" years, well, it's disheartening. Eventually, and I'll admit that this wasn't the smartest thing on my part, I just stopped going to my specialist. After several years, my haematologist suggested I go back to seeing my liver specialist. I tried, but I had to get referred again, and this time I got someone new.

They were quick to inform me of the *"new"* drugs, and how soon they thought they'd be available. Nothing I hadn't heard before; except this time it was months instead of years. So, naturally I was a bit more hopeful, but I really tempered that hope because I had been down that road before. The doctor's word turned out to be true though, and that was refreshing. So, one year after getting my new specialist, I was waiting for the new treatment. That waiting was a bit easier, I'll admit.

When I opened that package, cracked the lid on the jar and took out that first pill, I was, well, I can't easily describe it. I was both full of joy and afraid as well. Once I started taking the pill the only fear that remained was that I might be one of the small percent that it didn't work on; it could happen. Overall though my experience of this treatment was full of ups and almost no downs. The biggest *"down"* was having to remember to take it at the same time every day. Fortunately, I embarked on an artistic journey to help me remember: I took a selfie every morning of me taking the pill. Then, because I didn't experience any side effects, there were days I couldn't remember if I had taken the pill.

So, I just looked at my photos on my phone and checked to see if I had taken a picture on that morning. It definitely helped.

The weirdest part of this whole journey though has definitely been these last several months, months that I have been (technically) Hepatitis C free. I say weird because my life is no longer in immediate danger because of this horrible disease and yet I feel the same as I did before. I wasn't experiencing any symptoms of having Hepatitis C and so now that I still have no symptoms I feel, well, no different. Others around me though are ecstatic; and so I rejoice vicariously through them. As soon as I found out and shared the good news, a couple friends of mine began crying immediately. I was honoured and also a bit taken aback. Why wasn't I feeling this kind of intense release? Why wasn't I overjoyed? Why was I so neutral? It was (and still is) very confusing. As far as I can figure, it was because I had lived with Hepatitis C and the fear of it for more than 20 years, more than half my life. You don't end something like that without feeling something, and I think maybe I was feeling a bit lost; a part of me, a part of how others knew me, was gone (technically speaking). I think I was (maybe still am) grieving. It's hard to know exactly. I do know that everyone around me is excited for me and that is a very great gift!

I'm part of a generation of people with haemophilia who had to live with both, HIV and Hepatitis C. Beyond my surprise of being still here, to testify, I think I have a very complex relationship with my daily drugs/medicines.

Refusing to be a guinea pig, while accepting medical treatments, is part of my daily life. When the first treatments for Hepatitis C came on the market in the 90's, I accepted them, but only because I was compelled and forced to do so. It was a failure. The first treatment was very difficult to follow but bearable. During the next decade, the second combined Interferon and Ribavirin was awful. I thought I was going mad. After three months, I really got the strange/unsettling feeling of ingesting poison. A 48-week treatment that I wouldn't wish on anybody, not even my worst enemy and the virus was supposed to be eradicated. Two weeks after the end of the treatment, a blood test showed that the virus was still there, at the same level as before. I will remember it for a long time. It was 2 days before Christmas, I was alone in my kitchen, I opened the letter containing the results of my blood exams…. All for nothing!

When I heard there were new treatments available, I had my doubts and I was sure of one thing, never again would I take Interferon and Ribavirin. However, thirty years after being contaminated, my liver was starting to show some signs of failure. I was not that confident. I just didn't want to talk about it anymore.

Then, on one evening, as I was in Australia with a friend, directly involved by the matter, as we were having dinner together, an evening I'll remember for a long time… he asked me to reconsider my position. He told me how efficient the new treatments were, that they were much shorter, without or little side effects compared to the former ones. When I got back to my hotel, after this wonderful dinner, spent with someone caring for me and behaving like a friend, I read my emails and discovered the following message: *"Hi, I'm filling in forms to start treating my patients with the new treatments, without Interferon, for those who really need to treat their Hepatitis C. I truly think you should be part of those patients, that those treatments without Interferon are not complex to adhere to, and that you should give it a try. Do you want me to organise an appointment to undertake a thorough review of the situation? And by the way, how are you doing? Talk to me, answer me, let's do it, it's the right time to do so."*

You then realize that there are signs, and you accept those signs. This very same evening, two messengers changed my life. The first one looked me in the eyes, the second one sent me an invitation. The first one was a person living with haemophilia, the second one a physician. Both are friends.

Then, you probably know what happened next. I had a six month treatment. I didn't feel I was following one, and three months later, I got the confirmation that I was cured. The same week, I met the woman of my life, who stands today by my side. That would be the only side effect I could state, besides that… NO side effect, a disease eradicated within 2 weeks, and the rest of my life to enjoy it, keeping in mind that some of my friends were not as lucky as I am.

"When I heard there were new treatments available, I had my doubts and I was sure of one thing, never again would I take Interferon and Ribavirin".

I was diagnosed with contracting Hepatitis C genotype 1a in 1991, six years after been told the devastating news of being diagnosed with HIV. I was informed then that this virus would take anything from 20 to 30 years, before it would cause any real problems for my liver. Because there were no treatments or medication available, I feared at that time that HIV infection was the biggest threat to survival. Research and knowledge was also in short supply. In 1992 I was offered a course of Interferon treatment to clear the Hepatitis C and I agreed to do this. I spent ten months on this treatment without any success and was advised to stop as success was not achievable.

In 1997, new ARV drugs for HIV came on the market and once I went on these my HIV viral load levels fell to undetectable levels and so HIV became manageable and this still remains the same situation today. At the same time my Hepatitis C viral load was increasing causing further damage to my liver and now my real fears going forward was that this will be my major problem and life threatening. In 2002, I was offered the new dual therapy of Peg Interferon/Ribavirin. After 12 weeks on this therapy I had to be taken off it, as it was obvious that I was not going to be successful in clearing the virus, as I did not achieve the required two log drop in my viral load at that stage. This was very disappointing as my liver had moved from fibrosis to cirrhosis. It took another ten years for another form of treatment to come on stream in 2012. I was unfortunate that I could not avail of the triple therapy of Telaprevir or Boceprevir, along with Interferon/Ribavirin as my liver condition was so poor, that I would not tolerate this form of treatment, mainly because of side effects and infections that I would be exposed to.

Then in 2013, a tumour was discovered on my liver. My options were limited and I ended up having a liver transplant in April 2014. The transplant went better than expected and I made an excellent recovery, but the presence and threat of Hepatitis C remains. It is very timely in my case that the new improved therapies are available on the market and that they have a very high success rate for my genotype. I have my starting date for treatment as I write this article and I am very confident of success and look forward to life, Hepatitis C free. I have never refused any treatments offered to me as they became available but because they did not work in clearing the virus I ended up having to experience what this virus can do to the functions of the liver, poor health, poor quality of life to the point where I nearly did not survive. In my experience, I strongly advise taking this treatment if offered because to delay it, is to lead to more damage and maybe worse.

PERSPECTIVE 5

I have been waiting for the best part of 15 years to get a chance to get rid of Hepatitis C. Hepatitis C has caused me a lot of problems during that time, psychologically and personally. It was the reason why I have had to get a liver transplant, as I ended up developing a tumour in the liver. Waiting for a chance to clear Hepatitis C has been very frustrating, as I know if the virus starts to react it will attack my liver much more aggressively than it did the first time. With the new treatments, I am so relieved to know that there is a chance to clear it. Now I just can't wait, as I have the medication and will start in a few days. I just hope I don't find any problems while on treatment.

"I just can't wait, as I have the medication and will start in a few days".

PERSPECTIVE 6

It's 23 years since I found out I had Hepatitis C, but probably only three years since I realised what it means. I have cousins who have also had Hepatitis C and they received treatment seven or eight years ago, and they went through hell on it, one of them in particular had very bad reactions. I was just starting a career and I couldn't face it at the time and honestly I am glad I didn't. So I have put it to the back of my mind and ignored it because it was the easiest thing to do. It wasn't affecting me really. I may be a bit more tired or a little less focused but it's always been like that for me so I never felt an urgency to get treatment. Blood tests were slightly increased, liver results were good and the doctors said it isn't progressing and I didn't want to do the treatment for a year that might or might not work.

Four years ago, I met someone new and we have been together since. I didn't realise that I was putting things on hold. We have been discussing marriage, kids and the future. I now realise what I was doing probably wasn't the smartest thing to do. I want to move on and close that part of my life and I decided I was going to try treatment. When the doctors said there was a new treatment that was shorter and with less side effects and suggested waiting, I said I would put it on hold again. With this new treatment apart from it being more likely to

work, it would be shorter and easier. I also thought I would be able to continue working and I wouldn't have to tell anyone I was on it and I could keep it to myself. At the start I was ok with waiting. I had been waiting for years but I made the decision to close this part of my life as new treatments were coming soon. I have read about the groups that are getting treatment first. I know that's important and if my cousins needed treatment before me I would wait, but I am starting to get frustrated. I just want it gone. I want it over. I have made the decision and now it's at the front of my mind. Now I am thinking about it I can't stop and it's so close. I think it will be sometime next year, I just want a date!! From talking to people that have finished treatment I might not feel any different. I have been told it will add years to my life and that's what I want. I want as much time with my friends and family as possible and I want this out of my liver but more importantly out of my head.

AN UPDATE FROM THE AASLD LIVER CONFERENCE (San Francisco – November 2015)

The AASLD Liver Conference, took place in San Francisco in November this year and as always an enormous amount of new and interesting information was presented over the four days of the main conference on topics related to Hepatitis C.

The areas covered were on the benefits of treatment, the effectiveness of the currently available treatments, what is coming next and where the future is going. This article looks at some of the highlights from this year's conference.

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

BENEFITS OF TREATMENT

There was interesting information presented on the increasing prevalence of cirrhosis in adults with Hepatitis C in the US. They examined the rate of cirrhosis over three different time periods. From 1988-1994, the rate of cirrhosis was between 6.6% and 8.6%, depending on the scoring system used (APRI or Fib-4). Between 1999 and 2006, the rate of cirrhosis increased to between 7.6–10.2% of the population. This drastically rose between 2007 and 2012, where approximately 16-17% of the population with Hepatitis C had cirrhosis. This increase is associated with an ageing population. With these increases in people with Hepatitis C progressing to cirrhosis, the importance of treating early is becoming more important.

In relation to those who have been treated, with the new DAA regimens and have cleared the virus, one study presented data on the regression of fibrosis and cirrhosis. People were monitored with a Fibroscan every six months. The results showed that overall, 60% of people who achieved an SVR (cured) showed an improved result by a regression in the stage of liver damage, 34% remained the same and 6% got worse. When this was broken down, in those with bridging fibrosis (F3-4), 69% improved by a stage, 14% had no change and 17% got worse. The median time for regression to improve was 2.5 years. Furthermore, in those with cirrhosis, 55% of patients improved and 45% of patients remained with cirrhosis. The median time in this group for regression to improve was three

years. Another study, examined the effect of an SVR on complications associated with cirrhosis. Patients who were on DAA's treatments were compared to untreated or non-SVR matched patients. The rate of portal hypertensive complications in those who did not receive treatment or did not get an SVR was 49%, compared to 9% in those who achieved an SVR. The rate of patients requiring a liver transplant in the group who were untreated or did not achieve an SVR was 10% compared to 3%. Both of these results were statistically significant. In a French study, a cohort of 77 patients with cirrhosis who were on the liver transplant list and underwent treatment with the new DAA therapies, the results were that 84% achieved an SVR. They were followed-up after an SVR of between 12-95 weeks (mean 68 weeks), and 16% showed signs of improvement, giving them time to wait for a transplant and 18% were delisted from the liver transplant list.

Summary

- Fibrosis reversal is possible and follow up with a Fibroscan is a good method for patients to follow after achieving an SVR.
- SVR significantly reduces liver complications in those with compensated and decompensated cirrhosis.
- Treatment of patients on the waiting list for a liver transplant can result in improvements to create time for a transplant and in a minority of cases can result in delisting.

CURRENT TREATMENT REGIMENS - THE REAL WORLD

Genotype 1

There have been a number of multicentre studies examining the real world effectiveness of the new DAA regimens. Three of these are the HCV Target Study (969 patients), the TRIO study (895 patients) and the Veterans Association Study (VA) (3763 patients).

At AASLD, these studies showed results for treatment with Sofosbuvir/Ledipasvir (Harvoni®) in real world settings, to be 93-95% cure for those taking eight weeks of treatment and 96-97% cure rates for those on 12 weeks of treatment. The eight weeks licence is only available in the US and is limited to only to those who have never had treatment before, do not have cirrhosis and have a viral load less than 6million IU/ml. However, the preference appears to be to continue for the 12-week duration as is the license in Europe. In the HCV Target, TRIO and VA studies between 60%, 50% and 42% respectively, of the patients who received 12 weeks of treatment would have been eligible for eight weeks of treatment. These studies also looked at predictors for treatment failures. All of the VA cohorts were previously untreated, and 29% had cirrhosis. The main predictors in this group were African-American race, those with advance fibrosis and those receiving eight weeks of treatment. In the TRIO study, the predictors of failure in this group were the expertise of the centre the patients were being treated at, being of African-American race, having a low platelet count, the presence of cirrhosis and the type of DAA therapy used. In the HCV Target group, 53% were previously untreated, and 38% had cirrhosis. The main predictors of failure in this group were a low albumin level, elevated bilirubin and the use of PPI's at the start of treatment. A PPI or Proton Pump Inhibitor is a type of medication that is usually prescribed to reduce the production of acid in the stomach.

Summary

- SVR rates are similar to those seen in clinical trials showing high rates of success.
- Cirrhosis or advanced fibrosis is associated with lower success rates.
- Proton Pump Inhibitors, which can be prescribed for excess stomach acid, when used at the start of treatment results in lower success rates and other options should be assessed before starting treatment.

Genotype 3

In the ALLY 3 trial, Sofosbuvir and Daclatasvir was used for the treatment of genotype 3 and showed cure rates of 86-90%. However, this reduced to 63% in those with cirrhosis. A real world continuation study called the ALLY 3+ looked at

using Sofosbuvir and Daclatasvir with Ribavirin for 12 or 16 weeks in patients with advanced fibrosis or cirrhosis. In those with advanced fibrosis (F3), 100% of patients achieved an SVR for both 12 and 16 weeks of treatment. In patients with cirrhosis (F4), the cure rate was reduced to 83% for 12 weeks and 89% for 16 weeks. Previously being treated did not appear to affect the response significantly.

In the European Union, a compassionate use programme was looked at that included 102 people with genotype 3, who were considered at high risk of decompensation or death within 12 months, if they did not receive treatment, were treated with Sofosbuvir and Daclatasvir with and without Ribavirin. Most (85%) had liver cirrhosis, of whom 47% had Child-Pugh (CP) class A, 39% had class B, and 13% had class C. The group also included eight liver transplant recipients. The option to add Ribavirin was done at the clinician's discretion, and this was done in 39% of cases. The results showed 86% of the Sofosbuvir and Daclatasvir alone group and 88% who added Ribavirin achieved SVR12. Response rates were 91% without and 100% with Ribavirin for treatment-naive patients, and 82% and 81%, respectively, for those who were treated previously. SVR12 rates were 86% without and 71% with Ribavirin for the small number of people treated for only 12 weeks. Response rates for people with HIV and HCV co-infection were 83% without and 100% with Ribavirin, and all transplant recipients were cured either with or without Ribavirin, but these numbers were small. Response rates were about the same for people with cirrhosis treated with or without Ribavirin – 86% versus 88%, respectively – but there were some differences according to liver disease severity. Among those using Daclatasvir and Sofosbuvir alone, SVR12 rates were 100% for CP class A, 80% for class B and 75% for class C. Conversely, among those who added Ribavirin, response rates were 85%, 86% and 100%, respectively. The majority of patient's experienced adverse events, as expected for such a sick population, but treatment-related serious adverse events were uncommon (3% without and 5% with Ribavirin).

Summary

- SVR rates with Daclatasvir and Sofosbuvir with or without Ribavirin can achieve SVR rates of 85-90% in those with cirrhosis. This reduces with cases of decompensated cirrhosis to approximately 80%.
- The addition of Ribavirin or the extension to 24 weeks of treatment can be beneficial in patients with cirrhosis.
- Still room to improve on SVR rates for genotype 3 patients.

NEXT TO MARKET

The next two options for treatment coming to the market are:

- Elbasvir / Grazoprevir
- Sofosbuvir / Velpatasvir

Elbasvir / Grazoprevir

Early this year a large amount of information was presented on the combination of Elbasvir/ Grazoprevir at the EASL meeting in April, and you can read more about this in our last edition of Positive News. At AASLD, an integrated analysis of patients with cirrhosis was presented. Patients in the analysis were genotype 1, 4 and 6. All patients had compensated cirrhosis (Childs-Pugh Class A). Patients were included from the C-Worthy trial, C-Surfer Trial, C-EDGE Trial, and C Salvage Trial. As a result, there was some variation in treatment durations that included, 12, 16 and 18 weeks of treatment. In patients who were previously untreated, the addition of Ribavirin did not give any additional benefit. Patients who were previously untreated and received only Elbasvir / Grazoprevir for 12 weeks achieved SVR rates of 98% compared to those who received Elbasvir / Grazoprevir with Ribavirin, who achieved an SVR rate of 90%. In the treatment-experienced groups, patients who received only Elbasvir / Grazoprevir for 12 weeks achieved SVR rates of 89%. This increased to 91% with the addition of Ribavirin. When treatment was extended to 16 or 18 weeks, patients who received only Elbasvir / Grazoprevir without Ribavirin achieved an SVR rate of 94%, and this increased to 100% with the addition of Ribavirin. Overall there is a high efficacy across a broad spectrum of patients. There may be subgroups that require longer therapy and potentially the addition of Ribavirin. This combination is expected in Europe in 2016.

Sofosbuvir / Velpatasvir (Sof/Vel)

There are four main trials being conducted on this regimen as it can be used on any genotype. The ASTRAL-1 trial evaluated Sofosbuvir / Velpatasvir for patients with all genotypes except 3, which has proven harder to treat with DAA's. All but two participants completed treatment. The overall SVR12 rate was 99%. Broken down by genotype, sustained response rates were 98%, 99%, 100%, 100%, 97% and 100%, respectively, for genotypes 1a, 1b, 2, 4, 5 and 6. SVR12 rates were the same (99%) for previously untreated and treatment-experienced patients, and for people with and without cirrhosis.

The ASTRAL-2 trial, which looked at a larger number of people with HCV genotype 2. This study compared treatment with Sofosbuvir / Velapatasvir with the current standard of care for genotype 2 of Sofosbuvir with Ribavirin for 12 weeks. SVR12 rates were 99% in the Sofosbuvir / Velpatasvir arm and 94% in the Sofosbuvir plus Ribavirin arm. SVR12 rates with Sofosbuvir / Velpatasvir were similar for treatment-naive and treatment-experienced patients, and for those with and without cirrhosis.

The ASTRAL-3 trial focused on people with HCV genotype 3. About a quarter were treatment-experienced, and 30% had cirrhosis. Patients received either Sofosbuvir / Velpatasvir for 12 weeks or Sofosbuvir plus Ribavirin for 24 weeks. All but two Sofosbuvir / Velpatasvir recipients completed treatment while 21 in the Sofosbuvir plus Ribavirin arm dropped out early. SVR12 rates were 95% in the Sofosbuvir / Velpatasvir arm and 80% in the Sofosbuvir plus Ribavirin arm. Response rates with Sofosbuvir / Velpatasvir were similar for treatment-naive and treatment-experienced patients (97% and 90%, respectively), and for people with and without cirrhosis (91% and 97%).

Finally, the ASTRAL-4 trial, examined patients of all genotypes with decompensated liver disease. This trial included 267 patients with Child-Pugh-Turcotte (CPT) class B, indicating a 20% risk of death in the next year. About 60% had genotype 1a, 18% had 1b, 15% had genotype 3, and less than 5% had genotypes 2 or 4. Just over half were treatment-experienced. Overall SVR12 rates were 83% and 86% for patients treated with Sofosbuvir / Velpatasvir for 12 or 24 weeks, respectively, rising to 94% for those who added Ribavirin. Looking at just genotype 1, the corresponding SVR12 rates were 88%, 92% and 96%. Response rates were lower for genotype 3 – only 50% using Sofosbuvir / Velpatasvir alone for 12 or 24 weeks, and 85% with Ribavirin. Everyone with genotype 2, 4 or 6 were cured except one genotype 2 patient who died of liver failure.

FUTURE THERAPIES

The aim that all treatments in the future are striving for are:

- Pangenotypic - One-size fits all and no need to worry about genotype.
- No need for Ribavirin.
- High barrier to resistance to prevent relapse of viral breakthrough.
- Short Duration (8 weeks or less) – This could lead to lower cost, improved adherence, reduced emergence of resistance and overall simplicity of treatment.

The SURVEYOR-1 study assessed the effectiveness and safety of two experimental next-generation Direct Acting Antivirals ABT-493 and ABT-530, which both pangenotypic. The study recruited 79 previously untreated people or previous null responders to pegylated Interferon and Ribavirin, all with genotype 1 infection and no evidence of cirrhosis. After 12 weeks of treatment, SVR rates 97- 100%. One patient relapsed after, and all treatment-experienced patients achieved SVR12.

In a subsequent phase of the SURVEYOR-1 study, 34 participants with genotype 1 received eight weeks of treatment, 97% (33/34) achieved an SVR12. On the basis of these results, this combination will be tested in 8 and 12-week regimes, in six phase 3 studies due to start in December 2015.

The SURVEYOR-2 study recruited previously untreated people or previous null responders to

pegylated Interferon and Ribavirin, with no evidence of cirrhosis. Twelve weeks after the completion of treatment, SVR12 rates ranged from 83% to 93% in the two Ribavirin-sparing arms and 94% in the Ribavirin-containing arm. The study also contained a genotype 2 population. SVR12 were very high ranging from 96% - 100%.

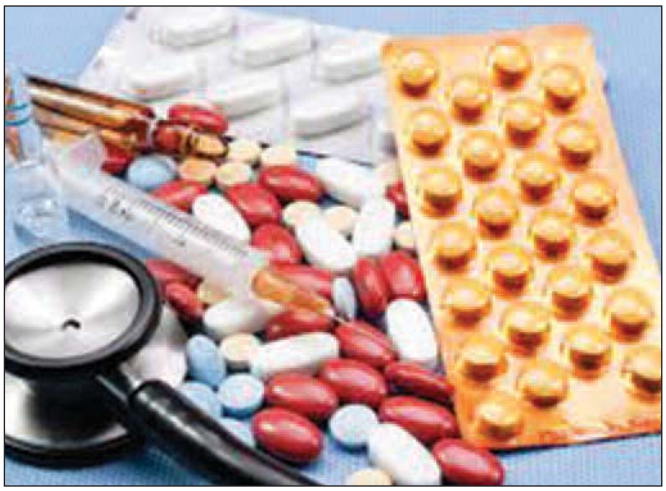
CONCLUSIONS

- **Currently approved treatments achieve SVR rates in the real world similar to those achieved in the clinical trials.**
- **Large real world studies are identifying the factors associated with failing treatment.**
- **There is increased availability and success of therapies in traditional and new difficult to treat populations.**
- **The effects of Hepatitis C resistance associated variants needs to be monitored for the improvement of treatment in some populations.**
- **There is an exciting pipeline that is focused on being pan-genotypic, safe, have high efficacy and have shorter durations.**

DIFFICULT GROUPS – WHO'S LEFT?

When the only treatments that were available were Interferon and Ribavirin, the cohort of people that could be treated and cured was minimal. Firstly, those with genotype 1 achieved cure rates of about 40% or less in those who were able to complete treatment. Genotype 2 and 3 were considered the easiest to treat with higher cure rates. Other groups that were more "difficult-to-treat", where those who had been treated before, that had virus breakthrough on treatment, relapsed afterwards or those who had no response to treatment at all. Also, people who had other conditions were also restricted due to issues associated with Interferon. For example, those with HIV co-infection did not generally respond as well as those with Hepatitis C only. There were also interactions with other medications that they were taking. Patients who required a liver transplant also had difficulties with treatment as Interferon put a strain on the new liver. Finally, for those with cirrhosis, if treatment was possible, it generally was not as successful.

In the era of Direct Acting Antivirals (DAA's), this has completely turned this paradigm upside down. Now people with genotype 1 are no longer the most "difficult-to-treat" group with almost all treatments achieving cure rates in excess of 90%. Relatively early on with the new



treatments, those who failed on Interferon-based treatments previously by virus breakthrough or relapse were, no longer a challenging group and over the last year even those who were null responders on Interferon-based treatments as a group have become significantly less challenging. The treatments are so effective that even those who failed on first generation DAA's are now successful. People with liver transplants and those with HIV co-infection have even lost the tag of "difficult-to-treat" with results almost identical to those with Hepatitis C only. The only consideration these two groups are getting is a prioritisation for treatment as the progression can be faster apart from drug interactions and hence

treating sooner rather than later is a better option.

So who is left in the “difficult-to-treat” groups and what is the definition? Amazingly the definition of “difficult-to-treat” is results where cure rates are less than 90%, which is an astounding change compared to where we were even three years ago.

There are a couple of sub-groups that still remain a challenge. Firstly, while those with compensated cirrhosis have responded very well to DAA treatments, there are some challenges with those who have decompensated cirrhosis. Of the currently available some not recommended for use in Childs-Pugh Class C cirrhosis, which restricts the options and assessments in Europe are ongoing for Childs-Pugh B and the uses of some regimens. For those with decompensated cirrhosis, across clinical trials and real world data there is a wide variation in success with cure rates ranging from 56 -100% depending on genotype, Childs Pugh Score, MELD Score and treatment regimen. This variability is significantly higher than what has become the expected variation of 90-100% in those without cirrhosis or those with cirrhosis of Childs-Pugh Class A. Optimisation of currently available as well as upcoming treatments is on-going. There is also a lot of discussion around people with poor livers, who are in limbo.

The second cohort that remains “difficult-to-treat” are genotype 3. This genotype is associated with faster progression to cirrhosis and liver cancer. Originally these people were listed with the easier to treat cohort. However, this is becoming sub-divided. Those who have never had treatment previously and do not have cirrhosis are achieving cure rates in the 90-100% range. This drops slightly in those who have been treated previously. However, there is a significant drop in success rates when cirrhosis is present for genotype 3 patients with a range of success rates from 47-86%. New treatments currently in the pipeline are producing better results but the main focus to improve cure rates in this “difficult-to-treat" group is to treat early before cirrhosis starts to affect the chances of success.

The next “difficult-to-treat” group are a relatively small number of patients with renal disease. Again Hepatitis C can be a significant additional complication in these patients and removing the effects of the virus in this group is very beneficial. Currently, there is only one treatment that is not metabolised through the kidneys. Safety data is coming through using other currently available regimes as well as the problems associated with controlling doses of Ribavirin for those with renal disease. New regimens coming in 2016 will be beneficial for this group of “difficult-to-treat” patients.

The final group that is “difficult-to-treat” is the smallest yet slowly growing group of those that have failed the new DAA treatments. For this group the majority of the questions are based around the initial treatment, specifically if the duration of treatment was long enough or was Ribavirin used, or was adherence an issue, was there other drug interactions that were not accounted for. When all of these areas are assessed the question of Resistance-Associated Variants (RAV’s) becomes important. This is where there are slight variants of the same virus genotype present when starting treatment. There may also be multiple variants that can cause some further issues. In this case, testing before re-treatment may be done and a multi-drug approach used with three or even all four different drug types being required to achieve a cure. Furthermore, newer treatments in the pipeline have higher barriers to resistance that may also have an impact reducing the number of DAA failures on the first treatment.

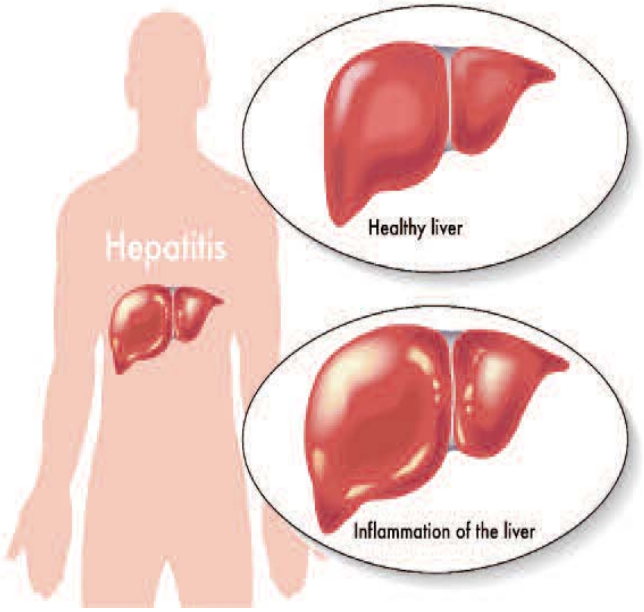
The definition of “difficult-to-treat” patients being less than 90% is an amazing leap forward in the last few years. The now “difficult-to-treat” groups, including those with decompensation, genotype 3, renal disease and those who have failed the current DAA treatments are the reminders, that there is still some work to do in the area of treatment optimisation of currently available regimens. One of the key components to all of these is earlier intervention when additional complications are not present. For those who this is not an option for, multiple new combinations will be available in the near future.

RIBAVIRIN – THE UNWANTED PHOENIX

The era of Interferon is dead for those using Direct Acting Antiviral's (DAA's) regimens. In almost every genotype currently available, treatments are the same or better without Interferon. However, the era of Ribavirin continues, despite persistent attempts by clinicians to remove it from regimens. Ribavirin adds benefit to the treatment if it is being prescribed. This article looks at issues reported by people on treatment, the significant difference between side effects of old treatments compared to current ones and how this affects the use of Ribavirin and options to reduce the already minimised side effects if they occur.

At the AASLD Conference in San Francisco, Ribavirin was referred to as the unwanted Phoenix, that clinicians are trying to burn, but it keeps rising, or, my personal favourite, *"the unwanted house guest who just keeps paying the bills"*. In all currently available treatments, and in particular in those who are "difficult-to-treat" cases, Ribavirin continues to add some benefit. The reason for this benefit is a little unclear as the exact mechanism of how Ribavirin works is unknown. One of the theories suggested at the conference was that the Ribavirin reduces the development of resistance associated variants (RAV's) of the virus. This means the DAA's are doing the job they were designed to do, i.e. stopping the virus replicating. At the same time, the virus is trying to change itself so that it can continue to replicate in a slightly different version of itself and hence become resistant to the DAA's. It is then suggested that the Ribavirin affects these different versions making them not as stable and hence the virus is less likely to develop resistance.

However, at the moment, it is still very much used, and it does add benefit if it is prescribed. Many people may be wary of Ribavirin from the past treatments when it was combined with Interferon. The combination of side effects was very difficult to deal with on that treatment. However, the use of Ribavirin with DAA's is much more tolerable with the most common side effect being fatigue, headache, anaemia, itching and rash. In comparison to the old treatments when Interferon and Ribavirin were together, using the new treatments, there is a significant difference in how often these side effects are even reported. There is almost a 40% reduction in people reporting



headache and fatigue and a 52-70% in the anaemia, rash and itching. Even when these are reported they are much milder than in the treatments with Ribavirin and Interferon and the numbers of people stopping as a direct result of side effects are minimal.

However, if you do get side effects from Ribavirin that are difficult (this is becoming rarer), there are options. You should contact your treater and have a conversation with them about potential options. Firstly, you and your treater should talk about what the issues are as there are many options that are available to minimise side effects. For example for the itching, drinking a lot of water, using unperfumed toiletries and using a moisturizer alone can reduce any potential itching considerably. If it is persistent, there are creams that can be prescribed that can help. These are the first line options. If it persists, there may be another alternative. In some clinical trials, they start at a regular dose of Ribavirin and then reduce it. Less commonly, clinical trials have looked at starting low and working up to a tolerable level. The discussion about any changes is very dependent on your current clinical condition, your level of liver damage, how you responded to treatment previously as well as other factors to get the best outcome for treatment.

Overall if Ribavirin is prescribed the benefits by far out way any negatives in the long run and there are options available in different forms to you when completing a treatment where Ribavirin is involved.

At a session at AASLD, on the global treatment of how new Hepatitis C treatments are being accessed in different regions of the world, there were some interesting discussions.

In the US, there are about three - four million people with Hepatitis C, and about 50% of these are screened and diagnosed. Of those who have been diagnosed, referral to a treatment provider happens between 40-60% of the time. In the Interferon era, very few people were eligible for treatment, and a limited proportion of them were cured. In the current Direct Acting Antiviral (DAA) era, therapy is not limiting the amount of people that can take treatment but access is limited to those who treatment will be reimbursed to, due to cost. In the US as in many countries there have been several advancements in the overall treatment of Hepatitis C. From a diagnosis perspective, by being diagnosed earlier, transmission routes are being interrupted by good intervention programmes such as needle exchange. There is increased efforts in relation to a screening strategy. From a treatment perspective, the use of non-invasive assessment tools, (such as a Fibroscan) are being used more commonly and effectively. Regimens for treatment are Interferon-free and moving towards Ribavirin free. There is a dramatic improvement as well. In results that are being achieved moving from the 40% cure rates to 90%. Even in the "difficult-to-treat" groups there has been vast advances in curing the majority of these patients. There are also up to date treatment guidelines that are keeping pace with the changes in these advancements for new treatments. The biggest challenges going forward are improvement of screening programmes, referral to appropriate care pathways and access to treatment (primarily focused on cost). In 2014, $12.3 billion was spent on drugs for Hepatitis C treatment up from almost $1 billion in 2013 and the demand for access is increasing.

From a European perspective, there is a wide range of diagnosis rates and treatment rates

across the European countries. In relation to access to Interferon-free treatments, Western countries have been reporting better access in recent months. However, access is still very restricted, if access is even available. In Asian countries, the rate of infection in Pakistan is 5% and Mongolia is 15%. There is also greater diversity in relation to the genotype that is prominent across the different areas of the continent. The access to Interferon-free therapies is very slow to be taken up. In 2014, Hong Kong, Japan, Taiwan and Turkey had access to the first generation of DAA treatments that were still used in conjunction with Interferon. Japan, Hong Kong, Korea and Malaysia were getting limited access to Interferon-free regimens this year. A similar situation on access to new drugs is also seen in Latin America. The speed of expected approval for these treatments from 2016-2018 is expected to improve as many of the companies are working at developing programmes in these regions for those countries with a low income to improve access with generic licensing, planned programmes and reduced prices.

The most interesting case study on dealing with the burden of Hepatitis C is the Egyptian story. The population prevalence of Hepatitis C is about 15% of the population and can be as high as 25% in some of the areas of the country. In 2006, Egypt developed a National programme for the treatment of Hepatitis C. It developed a network of 26 centres specialised in the treatment of Hepatitis C. Between 2006 and 2014, 360,000 people were treated for Hepatitis C. It was 48 weeks of Interferon and Ribavirin with success rates less than 50% and cost per treatment around $2,000, with an annual budget allocation of $90m. In 2014 and 2015, the Egyptian government signed deals to improve access to the new DAA treatments. The treatment was 12 weeks of treatment with Interferon and DAA's, or for those who could not tolerate Interferon 24 weeks of treatment with DAA's. The treatment group like in many countries around the world was limited to the sickest at first, and only those patients with cirrhosis were treated initially. By October 2015, there were over 1.1 million people registered and the programme was increased to 42 centres. In the last year alone, 134,654 patients (12%) have been treated with cure rates between 67-86% and the budget has remained the same at $90 million.

One of the interesting aspects of this session was a discussion on the roll out of Hepatitis C treatments. In the US, as a result of treating those with cirrhosis and the success of treatment, the new treatment guidelines have removed the prioritisation of those with cirrhosis and recommended that treatment should be made available generally to all patients. In the European guidelines, when they were reviewed at the start 2015, they increased the scope of who should be prioritised after the cirrhosis patients and at the speed of advances in the field it is likely that the next guidelines may follow their counterparts and recommend general treatment. Even the Egyptian programme is removing their prioritisation for 2016 and opening treatment to all patients. While there is varied access across different countries, in many parts of the world, this is a very good lesson on where all countries should be at this stage. Having a centralised budget with defined centres for treatment and having a strong treatment mandate to treat as well as negotiating good prices, countries in 2016 should be able to commit to treating much larger numbers of the Hepatitis C population.

The World Health Organization (WHO) is developing a global Hepatitis C strategy, that has as its goal the elimination of Hepatitis C as a major public health threat. Globally, there are 80-170 million people with Hepatitis C and 13-34 million are expected to have cirrhosis. The plan lays out a pathway of what is needed by a health system to scale up Hepatitis C treatment. In the plan using estimates of $10,000 per treatment for high-income countries and $500 per treatment in low and middle-income countries, the expectation that between 2016 and 2020 the global cost of treatment, prevention and other costs will grow from $5billion in 2016 to almost $30billion in 2020. While costs per current treatments have not reached these levels yet; the strategy is very welcome and the hope for eradication of Hepatitis C is closer than ever.