The ’R’ Word: The Sad Reality of Relapse

July 28, 2016 By Greg Jefferys

The issue of relapse after treatment with the new Hep C drugs like Harvoni is not much discussed, I guess because we like to focus on the positive, the incredible cure rates, the happy news of another person reaching SVR 12 or SVR 24.

Yet whilst the new Hepatitis C treatment using Direct Acting Antiviral drugs (DAAs) has given incredible cure results for vast numbers of people with Hepatitis C the sad reality is that about one person in every 33 people who start treating their Hep C with the new DAAs will relapse after their treatment ends.

It does not matter if the treatment was with generic Hep C meds like Safino-L or Ledifos or Darvoni or the brand versions like Harvoni or Sovaldi the relapse rate is the same. The success rate for all genotypes except genotype 3 is about 96%. Hepatitis C genotype 3 has a slightly lower success rate of about 90%.

So the big question is: “Why does one person relapse when the other 33 did not?”

This is literally the billion dollar question.

It is a big question for me, having completed successful treatment, having gone through the waiting period of wondering if I had cleared. The anxiety after the blood test to see if I had cleared the virus and waiting to hear the results. The 4 week blood test, the blood test at the end of treatment and the blood test 12 weeks after the end of treatment.
With every test was the anxiety. Particularly waiting for the results of 12 weeks after end of treatment blood tests. This is the SVR 12 test. If a person has no detectable virus in their blood 12 weeks after the end of treatment they are officially cured.

Its a big thing, and a big relief if you get the good news.. If you are clear 12 weeks after the end of treatment then you are cured, but if the virus has come back then you are shattered.

That is what I want to talk about in this post. I want to talk about relapses because for every 30 or so people who send me a joyful, exuberant email telling me they are clear I get one email telling me the sender has relapsed.

And it breaks my heart.

The reality is that there are a number of possible reasons for a person with Hep C to relapse but no-one knows exactly why some people relapse and others don’t, all we know is that there are a number of factors that could cause a person to relapse.

So what is relapse? What does it mean?

Well basically to relapse means that the treatment did not kill every Hep C virus in your body. That hidden somewhere in your body, usually in scar tissue in the liver, one or two or three virus remained alive, the medicines did not reach them where they hid.
When treatment ends and the DAAs leave your system these few remaining virus start to reproduce again and very quickly their numbers will rebuild. In the 12 weeks between end of treatment and the SVR 12 test virus numbers can go from undetectable to 3 million virus in a unit of blood. That is billions and billions of virus once more living in your blood.

So a person can have undetectable levels of virus from as early as week four of treatment but if just one hidden pocket of virus remains when treatment stops then a relapse will almost always result. (not always be usually).

What are the causes of relapse?

As mentioned this is the big question. Certainly people with severe cirrhosis seem more likely to relapse. For this reason it has become a common practice by specialist doctors to extend the length of treatment time for people with severe cirrhosis. Usually people with cirrhosis require 24 weeks treatment not the normal 12 weeks.
Because cirrhosis involves scar tissue in the liver the virus can live in the scar tissue where the DAAs have difficulty reaching because there is very little blood circulation in scar tissue.
The Hep C medicines are carried in your blood, where there is not much blood flow then the drugs do not saturate the tissue easily.
So if you have cirrhosis you should discuss with your doctor whether you might need a slightly longer treatment.
This is certainly the case for genotype 3, which has proven the hardest Hep C genotype to remove.

But there may be other causes for relapse as well.

One of these is UNDERDOSING, the opposite of overdosing.

Harvoni and Magnesium

Sofosbuvir and Ledipasvir (Harvoni) and Daclatasvir are both absorbed primarily in the stomach. Sofosbuvir is quite soluble, it dissolves easily in the stomach, same for Daclatasvir. However Ledipasvir does not dissolve easily. It does dissolve but not easily. For this reason Gilead advises against taking antacid within 4 hours before or after taking Harvoni. So an 8 hour period where no antacid should be taken.
Below is the exact warning from Gilead:

“Avoid taking an antacid within 4 hours before or 4 hours after you take Harvoni. This especially includes antacids that contain aluminum or magnesium (Acid Gone, Aldroxicon, Alternagel, Di-Gel, Gaviscon, Gelusil, Genaton, Maalox, Maldroxal, Milk of Magnesia, Mintox, Mylagen, Mylanta, Pepcid Complete, Rolaids, Rulox, and others”

It seems likely that that stomach acid assists in making the Ledipasvir soluble and that anything that

neutralises the stomach acid might reduce the amount of Ledipasvir that the body absorbs, possibly resulting in an underdose of Ledipasvir.

You will notice a heavy emphasis on not consuming magnesium, interestingly the world famous Mayo Clinic also suggests avoiding magnesium during treatment with Harvoni.
In the past couple of months I have begun the habit of asking people who have written to me telling me that they have relapsed if they are taking any dietary supplements. Several of them have responded that they have been taking magnesium supplements.
Now whether this is a factor in their relapse of not I do not know but it is worth considering.

Taurine, Caffeine and Daclatasvir

In my post on 21st February 2016 I discussed the discovery of Dr James Freeman that taurine, a common ingredient in energy and body building drinks, affects the absorption of Daclatasvir, because Taurine modulates induction of an enzyme called cytochrome P450 3A4 mRNA by rifampicin in the HepG2 cell line.

In plain English this article tells us that Taurine increases the levels of the enzyme CYP3A4. This is the enzyme that removes Daclatasvir from your system - in other words if you are consuming Taurine the effect is like you're taking a 1/2 dose, or maybe even a 1/4 dose of Daclatasvir because taurine will reduce the affect of Daclatasvir significantly!

This in turn will mean that your chances of clearing the virus are reduced significantly.

Now taurine may not be the only thing that causes the body to remove Daclatasvir at increased rates, each and every "... extract" will contain dozens of chemicals, all of which might induce or inhibit CYP3A4.

For example the body uses the enzyme cytochrome to break down caffeine so it might be that high levels of coffee consumption causes elevated cytochrome levels that in turn will effect the amount of Daclatasvir the body can use.

One of the things that ties in with relapse is the slow responder.
I was contacted by a lady today who is a slow responder using generic Harvoni and had not reached undetected by 8 weeks. I asked her if she was taking any supplements or other medication and the only medication she is taking is a sleeping tablet, Zopiclone.
Interestingly when I googled Zopiclone + Harvoni I found a paper immediately that mentioned the CYP enzymes again. (Remember CYP3A4 which is the villain for Daclatasvir)

Zopiclone is also metabolized predominantly by CYP3A4 and to a lesser degree by CYP2C8 and CYP2C9. Zopiclone concentrations may theoretically be increased by DAAs and require close monitoring. Most other benzodiazepines should be used cautiously in patients on DAAs. Clinicians may consider starting with a decreased benzodiazepine dose and monitoring for benzodiazepine-related toxicity, or selecting an alternate agent such as lorazepam, oxazepam or temazepam. Dose reductions are also recommended in patients with severe liver impairment as per product monographs

I posted this information in the Facebook group *Hepatitis C Treatment w/o Borders* and almost immediately got a comment from another person who was a slow responder and had relapsed. The only other medication she was taking during treatment was also Zopiclone!

Perhaps a coincidence? Perhaps not?
But here are those same enzymes again and it seems that maybe we need to be much more aware of drug interactions when using DAAs... particularly if there are issues with side effects and slow responding.

Conclusion
So what does all this mean. Basically avoid food supplements and “energy drinks” during treatment. Avoid magnesium and antacids. Closely consult with your doctor about possible drug interactions that might occur while you are treating your Hep C.
Avoid taurine and excess caffeine. (I am not saying stop drinking coffee but keep it to a minimum during treatment just in case.)

We only get one clear hit at Hep C treatment and we want to optimize our chances of clearing this virus so it is better to be safe than sorry.
If a person relapses there are still treatment options but lets see if we can avoid relapse and having to go through all that again!!!
