

Medical Writers' Circle

a series of articles

written by medical
professionals about
the management
and treatment of

Hepatitis C

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Patients with Hepatitis C: Who Should be Treated?



One may wonder why this question is being asked, as surely if one has hepatitis C, and a treatment is available surely treatment would naturally be recommended? But unfortunately, although the success rates with anti viral therapy for chronic hepatitis C have improved markedly over the last ten years, a cure still cannot be achieved in everyone, the current therapies still carry with them many side effects and there are still many infected individuals who have contraindications to their use. So some judgment has to be exercised regarding who will benefit most from therapy and who may suffer untoward consequences of therapy that could shift the risk: benefit ratio in the wrong direction.

Current Standard of Care for the Treatment of Hepatitis C

The most effective anti viral therapy regimen is a combination of long acting, Pegylated Interferon alpha + the oral nucleoside analogue Ribavirin. A sustained virological response (SVR) which is defined as undetectability of HCV RNA in the blood both at the end of treatment and six months after cessation of therapy, occurs in

54-56% of individuals given this treatment. As with earlier forms of anti viral therapy, the response rate is very much dependant on the particular genotype of the Hepatitis C infection.

Factors Influencing the Anti Viral Response

As with all other anti viral therapies for hepatitis C, the particular **genotype** of the infecting virus has the greatest influence on the sustained virological response to therapy. In those individuals infected with genotype 1, the expected SVR ranges from 43-46% and in those with genotype 2 or 3 infections, from 76-82%. Other factors influencing this response include the height of the **viral load** (the higher the viral load, the lower the SVR), the **severity of liver disease** (individuals with cirrhosis have a somewhat lower overall response rate, 43-50%), **body habitus**, the heavier the person, the lower the response rate.

Absolute Contraindications to Pegylated Interferon and/or Ribavirin Therapy

Interferon

Interferon is a natural cytokine produced whenever a viral infection is present, and when given by injection, typically

causes flu-like symptoms. However Interferon has some much more serious untoward effects which make it an unsuitable drug in certain individuals. It may impair bone marrow function. Red and white blood cells and platelets are all made in the bone marrow and so individuals who already have low values for any of these blood components may not be able to tolerate Interferon therapy safely. A low white count and/or low platelet count is particularly common in individuals who have already developed cirrhosis of the liver. Other concomitant medications may lower the hemoglobin, e.g. anti viral treatment for HIV, and it is for this and many other problems with drug interactions that makes treatment of hepatitis C in individuals co-infected with HIV is so problematic.

Interferon may affect the brain, which is why it is not given to individuals who have a seizure disorder that cannot be controlled with anti-epileptic therapy. Nor is IFN therapy thought wise in an individual who suffers from depression unless the latter is controlled with anti-depressant therapy. Interferon can also cause arrhythmia's of the heart, and thus individuals that have had cardiac irregularities may be unsuitable for Interferon therapy.

Interferon is a very potent immune stimulant, which is one of the reasons why it is so effective in viral hepatitis, but in individuals who already have some immune disorder, particularly those with autoimmune disease, e.g. rheumatoid arthritis, systemic lupus erythematosus, it is unwise to use Interferon for

from hardening of the arteries, should never be given Ribavirin.

Unfortunately, Ribavirin is also damaging to the unborn child (teratogenic), that means that neither a male or female may impregnate or conceive (as is appropriate for the gender) during treatment with Ribavirin and for six months after stopping

side effects continue throughout therapy. It is most important that treatment only be started during a relatively quiet and stable part of your life, i.e. not just prior to examinations, or just after taking on a new job. It is also unwise for couples living together who both require treatment to start treatment at

Ribavirin. When Ribavirin is added to Interferon therapy, it really does worsen the overall fatigue and depressant effect of this treatment.

What Can Be Done to Combat Side Effects of Therapy?

The really best outcome with anti viral therapies is when patients receive excellent nursing care. Because we know that the successful outcome of treatment correlates well with the individuals ability to take full course of treatment it is most important that those persons undergoing anti viral therapy are given as much help as possible, are forewarned about potential side effects and taught how to prevent them and how to deal with side effects when they are present.

As previously mentioned in those who have a tendency towards depression, pre-treatment with anti-depressants is advisable. This of course, needs to be by prescription from your primary care physician or psychiatrist. Planning to start treatment at a suitable time in your life is appropriate. For the first two weeks individuals are advised to take an extra strength Tylenol at the time of their injection and perhaps give the injection at bedtime. Because the Pegylated Interferon causes blood levels of Interferon to remain high all week, the episodic occurrence of side effects seen commonly following standard Interferon therapy given three times a week tend to be less. However, most patients find that the flu-like symptoms may last several days after the first few injections of Pegylated Interferon. If Tylenol helps, then this should be used for as long as is necessary, but no more than four

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fear of causing a flare up of the autoimmune disease. Neither can one safely use IFN with an organ transplant in place for fear of precipitating rejection (except if it is a liver transplant).

Occasionally Interferon, probably because of its immunological effect may promote liver failure leading to sudden and rapid deterioration in liver function. Thus no patient who has even the mildest evidence of liver failure should receive Interferon therapy.

Ribavirin

Ribavirin has two major side effects. It shortens the survival of red blood cells, which normally live 120 days. At least 1/3 of individuals given Ribavirin, have a markedly shortened red cell survival (called hemolysis). This may cause sudden onset of profound anemia, which leads to weakness and shortness of breath. Any individual who would become rapidly unwell with a sudden fall in hemoglobin, for example those who already have poor oxygen supply to their heart or to their brain

Ribavirin (Ribavirin lasts in the blood for 120 days after the last dose).

Ribavirin is excreted via the kidneys. Hence if there is any impairment of renal function, Ribavirin may be present in the blood perhaps even at high concentrations for a prolonged period of time, and this would enhance the likelihood of hemolysis, thus individuals with renal failure should not receive Ribavirin therapy.

Would Anti-Viral Therapy be Helpful for Me?

As long as you have none of the contraindications to either Interferon alpha and/or Ribavirin then it is reasonable to consider therapy for your hepatitis C. But there are also a number more factors that need to take into consideration before making the final decision.

Side Effects of Treatment

Treatment with Pegylated Interferon alpha and Ribavirin is not easy. Side effects tend to be maximal in the first two weeks of therapy, but in most, some

the same time. Fortunately, the initial flu-like symptoms of fever, muscle aches and headaches tend to diminish with time but most individuals undergoing therapy feel that they are under par for the entire treatment period, and some notice an effect on their mood such as becoming more irritable, occasionally developing overt depression. Whereas a past history of depression is no longer considered a contraindication to therapy, it may be wise in those who have such a history to consider going on anti depressant therapy prior to initiating treatment. Some individuals need to be started on an anti depressant during the course of their treatment. Other really irritating side effects include; dry itchy skin, cough, thinning of the hair, aphthous ulcerations of the mouth, diarrhea and insomnia. Skin reactions at the injection site is particularly common with the Pegylated Interferon. Weakness and shortness of breath are generally associated with the anemia caused by the

extra-strength Tylenol should ever be taken within a 24hour period, and should never be taken with alcohol. As alcohol elevates the viral load, it is wise to abstain completely from alcohol whilst undergoing anti viral therapy for hepatitis C. It is most important to consume large amounts (at least 3 Liters) of water daily during anti viral therapy. This markedly reduces the dry itchy skin, the skin rash, and sometimes even the nasal stuffiness. This quantity of water should be drunk on a daily basis from the first day of treatment. Most of the other side effects can be controlled by cutting back on the dose of either the Interferon or the Ribavirin. This may be either for the short-term or permanent.

New Stopping Rules

The good news is that if the viral load is measured just prior to starting therapy, and at twelve weeks into therapy, the physician can with a high degree of reliability predict whether or not treatment is likely to be successful. In those individuals whose viral load has not fallen by > 2 logs, they are advised to stop their anti viral therapy and as a consequence all side effects will rapidly disappear. In those individuals whose HCV RNA has fallen by 2 logs or more, continued therapy at full dose is advised. If however, because of adverse side effects the dose has to be reduced this does not seriously impair the overall response. Only stopping the drug completely after the first 12 weeks of therapy prior to completion reduces the chance of a successful anti viral response. Hence, if one passes the twelve week mark with a >2 log fall in HCV RNA it is really important to continue treatment for the full

term even if it has to be at a lower dose.

Should I Undergo a Liver Biopsy Prior to Deciding Whether or not to go for Anti Viral Therapy?

Mainly because previous anti viral therapy was < 50% effective was it recommended that a liver biopsy be done prior to deciding on treatment. This was because in those with very mild disease, it was considered quite safe to wait for better therapies coming along the pipeline and for those who were found to have more severe disease, any treatment that could improve outcome was thought worthwhile. What was looked for on liver biopsy was either a high degree of inflammation that predicted later development of scar tissue and/or an already high degree of scarring (fibrosis). It is now thought that perhaps in those with genotype 2 & 3 infections a liver biopsy may be more appropriate in those who are shown not to respond to the complete course of Pegylated Interferon & Ribavirin. However, in individuals with genotype 1 infections, the response rate is still <50% and so many patients opt for finding out whether or not they do in fact have evidence of progressive disease on liver biopsy before contemplating a full course of anti viral therapy. Unfortunately liver biopsy is the only way of diagnosing cirrhosis – it is very important to know if cirrhosis is present as this markedly affects both program and management.

Duration of Anti Viral Therapy

It is likely that those who have genotype 2 & 3 only need treatment for a maximum of six months, and half dose, i.e.

800mg of Ribavirin daily may be sufficient. The smaller dose of Ribavirin is associated with far fewer side effects. For those with genotype 1 infections and probably those with genotype 4, full dose Ribavirin and Interferon is required and for full 48 weeks of treatment.

Summary

It should now be possible for you to determine whether or not you should opt for anti viral therapy for your hepatitis C infection. Unfortunately there remain individuals who often for various non-liver reasons cannot tolerate current treatments. There are others whose disease is so mild and who have infection with a genotype that is more likely not to respond than to respond, who may opt to not initiate anti viral therapy at the present time. Unfortunately there will be some whose liver disease is too advanced for anti viral therapy to be safe and for some, a liver transplant may be the better option. ■

Medical Writers' Circle

is a program of the Hepatitis C Support Project.

The Mission of the Hepatitis C Support Project is to offer support to those who are affected by the hepatitis C Virus (HCV) and HIV/HCV coinfection.

Support is provided broadly, through information and education, as well as access to support groups. The (Project) seeks to serve the HCV community as well as the general public.

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