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Editorial

Treatment of relapser /nonresponder patients with chronic hepatitis C

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Chronic hepatitis C virus (HCV) infection has emerged as a leading cause of cirrhosis, liver failure, and hepatocellular carcinoma. The currently accepted primary end point of therapy is a sustained virological response (SVR) with the combination of Peginterferon (PegIFN) and ribavirin. This can be achieved in clinical trials[1],[2] and every day clinical practice[3] in 40%-45% of patients with HCV genotype 1 and 70% with genotype 4 treated for 48 weeks and in approximately 90% with genotype 2 and 70% with genotype 3 treated for 24 weeks.[1,2] SVR remains in 98% of the cases in the following 5 years and is considered as cure of the disease.[4]

Many patients who were non-responders to previous monotherapy or combination therapy are now considered candidates for re-treatment with the above more effective regimen. The major factors associated with the likelihood of an SVR following re-treatment include previous treatment regimen (conventional or PegIFN), infecting genotype, viral load and type of previous response. Non-responders to HCV treatment are not all the same. In some patients (10-15% of genotype 1, rarely seen in genotype 2 or 3) there is no reduction ($<2\log_{10}$) in HCV RNA on treatment (null responders), in others there is a $>2\log_{10}$ decrease in HCV RNA viremia at 12 weeks (early virological response –EVR [5]) but they never become negative (partial responders) and in others viremia disappears during treatment but it returns when therapy was stopped (relapsers, 20% of treated naove patients). Because partial virological responders and relapsers are more likely to respond to re-treatment than prior null responders, the HCV RNA levels should be monitored regularly in treated patients, until the pattern of response is clearly defined.

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial was a multicenter study of prior non-responders and relapsers to IFN monotherapy or to combination of classic (conventional) IFN and ribavirin with advanced fibrosis or compensated cirrhosis (the most difficult to be treated cases) [6]. A substantial proportion of treated patients (35%) became HCV RNA negative during re-treatment with PegIFN and ribavirin. Unfortunately, a large proportion of those relapsed when therapy was stopped, and SVR was observed in only 18% of cases. SVR was affected by race (Caucasian 20%, African American 6%), genotype (non-1 60%, 1 14%) serum HCV RNA level (< 1.5 million IU/ml 31%, >1.5 million IU/ml 6%) and fibrosis (no cirrhosis 23%, cirrhosis 11%). Patients with multiple poor prognostic factors had an SVR of only 6%. Failure to develop an EVR can help identify non-responders to re-treatment with a high degree of accuracy (ie, negative predictive value of 97%–100%). 35% of patients with an EVR went on to achieve an SVR, whereas an SVR occurred in only 3 patients (1%) without an EVR. In another study, prior IFN and ribavirin non-responders were re-treated with PegIFN and ribavirin for 48 weeks independent of their week-24 virological status, if they had a EVR. They showed an SVR of 10%.[7]

Patients with partial virologic response, or relapse could potentially achieve SVR if one or more correctable factors such as early dose reduction that contributed to the prior non-response are identified and addressed before and during re-treatment. Avoidance of dose reductions during the first 12 weeks of therapy or cessa-

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tion at any time during therapy improves SVR.[8] Furthermore, the EVR was significantly lower in patients whose ribavirin dose had to be reduced within the first 12 weeks of therapy, whereas the EVR was not significantly affected by reducing the dose of peginterferon during this same time interval. Ribavirin -associated anemia could be treated and alleviated with the use of epoetin alfa.[9] Neutropenia was not associated with infectious complications. Despite a mean baseline neutrophil count of only 3100/ mm^3, only 1% of patients enrolled into the study required dose reduction for bacterial infections.[6] In addition, no bleeding episodes occurred despite the fact that dose reduction was mandated only if the platelet count fell to 4O.OOO/m^3 or less during therapy.[6]

Other large multicenter studies (New York City - NYC Trial,[10] Evaluation of PEGIntron in Control of Hepatitis C Cirrhosis-EPIC[3 11]) of nonresponder/relapsers to IFN monotherapy or to combination of conventional IFN and ribavirin using 48 weeks of PegIFN and ribavirin have also demonstrated a similar with the previous studies[6,7] overall SVR rate with a high relapse rate (50%). In the NYC Trial, non-responders/relapsers to IFN +/- Ribavirin, when re-treated with PegIFN +ribavirin, had an overall SVR 16% (genotype 1 14%, non-1 33%, blacks 4%, /Caucasians 18%, non-responders to IFN monotherapy 21%, non-responders to IFN + Ribavirin 8%, relapsers to IFN + Ribavirin 42%).[10] In the EPIC[3] Trial, non-responders/relapsers to IFN +/- Ribavirin when re-treated with PegIFN+ribavirin, had an overall SVR 21% (56% in genotype 2/3, 14% in genotype 1, 41% in relapsers, 14% in non-responders).[11] In the last study, week 12 viremia negative patients had a relatively high SVR (57%).[11]

Patients with chronic HCV infection who were non-responders/relapsers to previous treatment with PegIFN and ribavirin are a growing population. The vast majority globally have genotype 1, a high viral load, advanced fibrosis or cirrhosis, and are of African-American race. The evaluation of these patients should include a thorough review of the previous treatment record and characterization of the previous non-response. A number of ongoing studies are also exploring strategies for re-treatment with the use of higher doses of PegIFN or ribavirin, for a longer period of therapy (72 weeks), or with a change of IFN (use of consensus IFN or another PegIFN).

Physicians should not hesitate to offer a 48 weeks re-treatment to patients who relapse after an initial, 24-week course of combination therapy, or who have prematurely stopped treatment. A 48-week course of PegIFN alfa-2a plus ribavirin induces an SVR in 55% of these patients.[12]

Prolonged suppression of detectable serum HCV RNA may help the immune system to clear the infected hepatocytes, as well as the extrahepatic reservoirs of HCV replication. At least 32 to 36 weeks of undetectable viremia by a highly sensitive molecular biology assay (Roche COBAS Amplicor 2.0® assay with a lower limit 100 IU/mL or even better transcription-mediated amplification assay-TMA®, Bayer Healthcare LLC, Tarrytown, NY with a lower cut-off 10 IU/mL) is probably required to attain sustained clearance of HCV in previously untreated patients.[13,14] Around 18% of HCV type 1 infected patients belong to the slow (late) virologic responders group (week 12 positive and week 24 negative).[14] This group of patients showed significantly improved SVR rates when treated for 72 weeks as a result of reduced relapse rates (45%). The improvement in SVR was most apparent in patients with genotype 1 versus other genotypes. The frequency of adverse events and dose reductions were similar in treated patients for 48 or 72 weeks.[15]

In the RENEW study, patients in low treatment response groups (overweight, fibrotics and blacks) treated with high-dose PegIFN 3.0 μg/kg weekly attained significantly higher SVR rates than patients receiving usual doses (1.5 μg/kg).[16]

High-dose ribavirin (ie, 800 to 1600 mg/d) with or without growth factors coupled with the increased side effects and costs of high-dose ribavirin and growth factors do not currently justify these approaches in clinical practice.[17] The frequency of treatment-related anemia is significantly lower for viramidine compared with ribavirin when used in combination with PegIFN alfa-2b in treatment-naive patients with HCV.[18]

A substantial proportion (45%) of PegIFN alfa-2b (12KD) /ribavirin non-responders achieve a virological response after 12 weeks when retreated with standard-dose PegIFN alfa-2a (40KD) plus ribavirin in the interim analysis of the REPEAT study.[19] The week 12 response rate was even higher (62%) among patients treated with high-dose (360 mg) PegIFN alfa-2a plus ribavirin induction therapy for 4 weeks. In these patients, the tolerability profile was similar to standard doses.

Nevertheless, antiviral therapy exceeding 48 weeks, high-dose induction with PegIFN and use of another PegIFN is not recommended in prior nonresponders and relapsers until the REPEAT study and others are completed and published as full papers and demonstrate an incremental benefit as well as an acceptable safety profile compared with 48 weeks of re-treatment.

Non-responders to conventional IFN plus Ribavirin were retreated with daily consensus interferon (CIFN-Alfacon®) 18 or 27 mg daily for 12 weeks and 9 mg/day always in combination with ribavirin. The SVR was 39% and 44% respectively for the non-responders to conventional IFN and 27% for the non-responders to PegIFN.[20] In another study, null responders to PegIFN plus Ribavirin who were re-treated with CIFN 15 μg daily plus IFN-gamma 1b 50 μg thrice weekly for 48 weeks had a SVR of 34%.[21]

Albumin interferon alfa-2b is a recombinant fusion protein of albumin and interferon alpha-2b with a longer half-life. In combination with ribavirin in non-responders to PegIFN, for 48 weeks, has an SVR of 20%.[22]

Patients with null virologic response and mild liver disease should be monitored without treatment until more effective therapy is available. SCH 503034 is a novel, oral HCV NS3 protease inhibitor. SCH 503034 plus PegIFN alfa-2b has potency against HCV genotype 1 in prior PegIFN alfa-2b nonresponders.[23] Valopicitabine is the first nucleoside HCV polymerase inhibitor. Valopicitabine plus PegIFN alfa-2a are more effective at suppressing HCV RNA than PegIFN alfa-2a/ribavirin retreatment in HCV genotype 1-infected patients with prior nonresponse to PegIFN alfa-2a/ribavirin.[24]

The options for patients with advanced fibrosis/stable cirrhosis not achieving SVR despite re-treatment are limited because they remain at increased risk for fibrosis progression to cirrhosis, decompensation, and hepatocellular carcinoma and may require liver transplantation in the near future. In cirrhotics, low-dose PegIFN-a for several years has been proposed as a way to prevent fibrosis progression and to reduce the risk of hepatic decompensation and hepatocellular carcinoma due to the anti-inflammatory, anti-fibrotic, and anti-carcinogenic properties of IFN.[25] The results are better when the viremia levels can be kept negative or at significantly reduced levels when compared with the treatment baseline.[25] This is a promising but unproven concept until the results of HALT-C [6] (90 mg PegIFN a-2a weekly), COPILOT[26] and EPIC[3 11] (0,5mg/Kgr PegIFN a-2b weekly) studies are published. Severely (bridging) fibrotics/cirrhotics relapsers or partial responders and patients with severe extrahepatic manifestations (i.e cryoglobulinemia, glomerulonephritis etc) regardless of the degree of fibrosis, may represent the groups of patients most benefited from maintenance therapy. For the time being, interim analysis of the COPELOT study showed a decrease of portal hypertension in treated patients.[26] It remains undefined which is the proper dose of PegIFN for maintenance therapy. Decompensated patients with ascites, variceal hemorrhage or encephalopathy are not candidates for maintenance therapy and should be offered a liver transplant. Maintenance pegylated IFN treatment is not recommended for prior nonresponders non-cirrhotics due to the associated toxicity, cost and uncertain benefit. Long-term PegIFN can lead to autoimmune side effects (thyroid diseases, diabetes mellitus etc).

Hepatitis C promotes insulin resistance and this in turn induces interferon resistance and fibrosis progression. The treatment of insulin resistance (with glitazones, metformin etc) could improve the SVR. In addition it has been shown, that reduction of weight can improve the liver enzymes and liver histology in patients without virologic response to therapy.[27]

In conclusion, considering patients for re-treatment should take into account the disease severity, the type, duration, and tolerability of prior treatment, and the likelihood of achieving a response with re-treatment. Non-responders to standard IFN +/- ribavirin should be considered for treatment with PegIFN plus ribavirin, whereas non-responders to PegIFN plus ribavirin for the same treatment if there was inadequate dosing, adherence, or monitoring or for longer duration therapy, i.e. 48 or 72 weeks for slow responders. Further attempts to cure HCV infection are most appropriate for patients who had relapsed after initial virological clearance or were partial responders. Many HCV nonresponders, especially those with no fibrosis or mild fibrosis, have an excellent prognosis, are at low risk to develop cirrhosis, and should simply be monitored at periodic intervals until more effective therapy is developed. Compensated cirrhotics could be started on maintenance long term PegIFN therapy at least if they were partial responders or relapsers to previous treatment.

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