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Editorial

Hepatitis C: are there any options for non-responders?

Nearly one half of *naïve* patients treated with the best available option (peginterferon plus ribavirin) remain uncured. Most of them are infected by genotype 1, and show insulin resistance and advanced fibrosis (1). The progression of fibrosis in non-responders remains unclear. Fibrosis after the first treatment improves in the majority of patients in spite of failed virological response. However, the influence of this "improvement" in the course of disease remains unknown. Recently, a cohort of 188 non-responders has been followed for up to 89 ± 25 months; in the second biopsy the authors often found a worsening of liver fibrosis, mainly in patients with lower platelet counts, AST/ALT above 1, or significant fibrosis (F2-F3) in the first biopsy. Moreover, 27% of patients became cirrhotic (2). Thus, non-responders are currently the greatest group of patients in our out-patient office; they are a group susceptible of fibrosis progression, and current therapeutic options remain suboptimal.

In the current issue of *Revista Española de Enfermedades Digestivas,* Carnicer et al. (3) report on the response to peginterferon alfa-2b plus ribavirin in a cohort of 124 non-responders. It is a very interesting study because data are reported from clinical practice, far from controlled trials, and the study is focused on the necessity of working together with several units to reach solvent conclusions. The overall sustained response was 30%, and a non-1 genotype and low viral load were found to be independent variables associated with sustained response, whereas the type of previous response, regimen (interferon alone or in combination with ribavirin) and fibrosis were not associated with response. Shiffman et al. (4) reported a sustained response rate of 18% in 604 patients retreated with peginterferon alfa-2a plus ribavirin, which was clearly different from that of the previous regimen and from virological response during the previous treatment, together with their genotype. Previous viral dynamics during treatment could strongly influence the possibility of achieving sustained response. Nearly 40% of patients achieving early virological response or viral clearance at any time (breakthrough), 50% of relapsers, and only 12% of "complete" non-responders became sustained responders when treated with peginterferon plus ribavirin. Indeed, the sustained response rate was 14% in patients infected by genotype 1 *versus* 54% for genotype 3, and 28% in non-responders to interferon alone *versus* 12% in non-responders to interferon plus ribavirin. In a cohort of 361 patients treated in clinical practice, sustained response was 70% in non-1 genotype relapsers to interferon alone and 19% in genotype-1 non-responders to combined therapy (5).

The difference between the work by Carnicer et al. and the latter two studies is not clear. The peginterferon used was different, cohort features were also different, and the low number of patients included in each group avoids reaching a statistical

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difference. Lastly, the virological response during the first regimen was unknown in the study by Carnicer et al., which could also be a bias.

The mechanism by which resistance to interferon develops is unclear. Viral, metabolic and genetic host factors have largely been implicated. Hepatitis C virus proteins may antagonize the antiviral activity of interferon alpha (6). The action of interferon is mediated by the Jak/STAT signaling pathway. Tyrosine kinases (Jak1, Tyk2) are activated after the interferon-receptor binding. The phosphorylation of STAT induces a heterodimer STAT1/2 that is translocated to the nucleus, leading to the formation of the interferon-stimulated gene factor 3 (ISGF3). ISGF3 ultimately leads to increased transcription of antiviral proteins such as 5'2'OAS, MxA and PKR. HCV proteins may induce interferon resistance by interacting with the signaling pathway at different levels. The PePHD site of the HCV E2 protein may bind PKR and abolish its kinase activity. Moreover, the carboxyterminal part of the NS5A protein may block protein synthesis *in vitro*. Lastly, HCV NS3/4A (serine-protease) may block the phosphorylation and nuclear translocation of interferon regulatory factor 3, thus resulting in a significantly reduced transcription of interferon genes. Thus, although HCV proteins induce interferon resistance by interacting with the signaling pathway, the definite regions of these interactions have not yet been defined.

Insulin resistance induces interferon resistance. The chance of achieving SVR in patients with hepatitis C infected by genotype 1 is 60% in cases without insulin resistance *versus* 30% in patients with insulin resistance (1). Besides, insulin resistance has been found in all groups of difficult-to-treat patients like HIV-coinfected patients, Afro-Americans, overweight subjects, and cirrhotic patients. In a replicon model, hyperinsulinemia has been found capable of blocking the interferon-mediated synthesis of antiviral proteins such as PKR and IRF-1. This effect seems to be mediated by the PI3K (phosphoinositide-3 kinase) signal transduction pathway (7).

Lastly, the genetic background seems to be different in responding *versus* non-responding patients. Several interferon-sensitive genes have been found to be up-regulated in NR. For example, an up-regulated USP18 (ubiquitin specific protease 18) gene was associated with lack of response to treatment with interferon (8). Indeed, the loss of USP18 expression in knockout mice was associated with interferon hypersensitivity. HLA B44 has also been found to be associated with sustained response to combined therapy (9). Thus, genetic background, insulin resistance, and HCV itself could be implied in interferon resistance, but the definite reason for failed response to interferon plus ribavirin is unknown.

On analyzing the results of re-treating with interferon + ribavirin patients who were non-responders to interferon alone it has been speculated that chances of achieving SVR in non-responders may be estimated as approximately the same as the difference in SVR rates between both schedules administered in treatment-*naïve* patients. Thus, patients infected with genotype 1 and who are non-responders to conventional interferon + ribavirin could, when treated with standard doses of peginterferon + ribavirin, achieve SVR in approximately 15% of cases (SVR_{Peg+R}: 46% - SVR_{I+R}: 31% = 15%). This theoretical piece of data has been confirmed by others (4,5). As such, the SVR rate achieved in previously-treated non-responders to combined therapy infected with genotype 1 remains sub-optimal when treated with standard-dose peginterferon + ribavirin.

At least three approaches have been postulated for the treatment of non-responders – triple combination therapy using amantadine, high-induction doses, and when viral eradication is not possible a longer-duration, low-dose peginterferon regimen.

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Triple therapy using interferon + ribavirin + amantadine has been assayed in non-responders. Contradictory results have been reported, and SVR has ranged from 0 to 48% in spite of similarly selected patients. An explanation is not available. Although some authors found a better response using amantadine hydrochloride *versus* amantadine sulphate, this result has not been confirmed. In a meta-analysis, SVR improvement was found to be around 8.3% (between 1.9 and 14.6%) when triple therapy was compared to interferon plus ribavirin (10). Thus, although interferon + ribavirin + amantadine may improve SVR rate in previous non-responders, such improvement is insufficient to recommend this therapeutic option in non-responders. Moreover, the main reason for the various SVR rates reported could be a selection bias in the group of patients enrolled, as well as the low number of patients included. A Spanish pilot study including 72 patients infected by genotype 1 who were previous non-responders to combined interferon-plus-ribavirin therapy were randomized into three different arms to receive peginterfon alfa-2a plus ribavirin 180 μg, 270 μg or 360 μg per week; results showed the same rate of adverse events with a similar tolerability, but sustained response was dose-dependent. Thirty-eight percent of patients treated with the higher-dose regimen achieved sustained response, *versus* only 30% of patients in the 270 μg arm, and 18% of patients in the standard 180 μg arm. The main difference between these three regimens is their relapse rates, five times lower in patients treated with the higher dose *versus* the standard or medium dose (11). Thus, induction therapy for at least 3 months using a double dose of peginterferon could be useful in the treatment of previous non-responders, achieving a higher sustained virological response rate owing to a lower relapse rate. Pilot studies using peginterferon alfa 2b (12) or consensus interferon (13) agree on a dose-dependent sustained response rate without increased adverse events. Currently a large trial including non-responders to combined peginterferon plus ribavirin is checking the usefulness of double doses of peginterferon for 72 weeks in achieving SVR. Other studies using low-dose peginterferon alone during 3.5 years are also ongoing. Final results from these studies are not available yet.

Therefore, genotype-1-infected non-responders belong to a very difficult-to-treat group of patients susceptible of faster fibrosis and devoid of useful treatment. High induction doses may improve sustained response, but a different approach is warranted to both eradicate the virus and stop fibrosis progression in chronic hepatitis C.

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