Current State of the Art Therapy in Genotype 2 and 3: Naive/Treatment Experienced

Keynotes
- The very high rates of SVR achieved by HCV genotype 2 and 3 with the standard treatment suggest a possible overtreatment.
- Why and in which patients we can recommend an Individualized treatment regimen?
- HCV genotype 2 vs 3 are not all alike
- Patients with unfavorable baseline characteristics are less like to achieve week 4 undetectable HCV RNA
- Higher dosages of ribavirin may increase the response rate in patients without RVR and in prior relapsers
- Future combinations are warranted to increase the response rates in treatment failures

Introduction
Treatment of patients with chronic HCV infection is undergoing powerful changes. The availability of Direct Acting Antivirals in patients with genotype 1 will limit the use of Peg-IFN and RBV only to subgroups of patients. Conversely, for patients infected with genotype 2 (HCV 2) and 3 (HCV 3), the impact of DAA-based therapies is currently under evaluation in experimental trials. Currently, the standard of care is represented by the dual combination of either Peg-alpha 2a and flat 800 mg RBV or Peg-alpha2b and weight-based ribavirin (1).

Treatment naive
This presentation will firstly discuss risks and benefits of the above standard regimens administered for a fixed 24 weeks duration in previously untreated patients versus those of an individualized treatment. Based on the evidences from a number of studies from European groups, EASL guidelines support the use of week 4 undetectable HCV RNA (RVR) as a key milestone on which to individualize treatment duration in HCV 2 and 3 (2).

However, there are specific rules to be followed in performing an individualized treatment strategy. Shortening the treatment duration to only 12/16 weeks, irrespective of RVR may lead to high relapse rates significantly reducing the efficacy of treatment (3). In the presence of cirrhosis the risk of relapse may be higher than after 24 weeks even in patients who resulted HCV RNA undetectable at week 4 (4).

To ensure efficacy rates comparable to those of the standard treatment, an individualized treatment regimen requires RBV dosages higher than the flat 800 mg, in particular in patients with HCV 3. (2,5)

Indeed, although HCV 2 and 3 have been combined together in the majority of the studies being more sensitive to Interferon-based therapies than HCV 1, they are not all alike (6). As shown in past and recent papers (5, 6, 8), SVR and RVR rates are lower for HCV 3 than for HCV2. These
differences find explanations in genotype-related epidemiology and pathogenesis. Accelerated progression of fibrosis has been shown in HCV 3. (7)

In the attempt to define, the subgroups of patients less likely to achieve SVR among those HCV 2 and 3 infected persons, different baseline predictors have been investigated. Among them, HCV 3, cirrhosis and viremia levels appear relevant, while the role of the unfavorable iL28B CT and TT genotypes has not been yet proven (8). It can be hypothesized that all of them concur to reduce the likelihood of achieving RVR.

As shown in the studies on HCV 2 and 3 performed from 2004 onward, the rate of response in patients without RVR is really unsatisfactory as it is lower than 50% (9). All the efforts should now be focused on these patients. A controversial area is the benefit of an extended course of treatment.

In previous relapsers after a short treatment course, longer duration has been shown to increase the response rate up to 70% (4), while in patients who relapse after a first standard course, response rates of 50% have been reported.

**Treatment Experienced**

Likely, the category of primary non responders among HCV 2 and 3 is very small, probably not higher than 5%-8% in genotype 2 and 3, respectively, in prior non responders there are so far limited treatment alternatives beside a re-treatment with the dual combination using ribavirin at the highest tolerated dosages for at least 48 weeks after the achievement of on treatment undetectable HCV RNA. In patients who failed to achieve SVR with a standard course, response rates after re-treatment may achieve 50%. Due to the limited number of these patients these evidence are empiric rather than based on controlled studies supporting strong recommendations.

**Future Therapies**

New treatment options are under evaluation. First generation PIs, telaprevir and boceprevir showed in vitro activity against HCV 2 and HCV 3, respectively. However, in vivo, these drugs are limited by side effects. According with a very recent press release, the combination of sofosbuvir and RBV for 12 weeks which ensures 97% rates of response in patients with HCV 2, showed the lowest rates of SVR 12 in HCV 3 subjects with cirrhosis and/or prior treatment experience (10). A combinations, including NS5A and NS5b inhibitors (daclatasvir and sofosbuvir) was also tested with promising results in previously untreated patients (11), however in this study presence of cirrhosis was an exclusion criteria.

**Conclusions**

In conclusion, satisfactory rates of SVR are currently achieved in non-cirrhotic patients with genotype 2 and 3 infection who receive a course of treatment with Peg-IFN and weight-based RBV for only 12/16 weeks, after RVR. Considering the costs of future combination treatment a 12 week course of Peg-IFN and RBV may spare costs with very limited side effects. In patients with genotype 3, response rates are lower than in genotype 2, in particular, in patients with unfavorable baseline characteristics who do not achieve RVR. All oral combination treatments are promising, although cirrhotic patients with genotype 3 might remain an unmet need.

**References**