Hepatitis C: The Impact of New and Future Therapeutics

Written by Phil Vinall

The burden of hepatitis C (HCV) in the United States now exceeds that of HIV and hepatitis B combined. It is estimated that from 2010 to 2019, 193,000 HCV-related deaths, direct medical care costs of $10.7 billion, and $75.3 billion in societal costs can be expected. HCV-associated liver related morbidity and mortality is an important component of this burden [Wong JB et al. *Am J Public Health* 2000]. Norah Terrault, MD, University of California, San Francisco, USA, discussed how antiviral therapy targeted to achieve viral eradication is the key strategy to stabilizing or reversing liver injury and fibrosis, and reducing the risk of liver-related complications, including cirrhosis and liver cancer, in patients with HCV.

Patients with genotype 1 were previously considered to be the poorest responders to treatment, but a recent study has shown significant increases in sustained virologic response (SVR) when these patients are treated with peginterferon plus ribavirin (PegIFN+RBV) plus a protease inhibitor (PI; boceprevir or telaprevir), whether they are treatment naïve [Poordad F et al. *N Engl J Med* 2011; Jacobson IM et al. *N Engl J Med* 2011] or have been previously treated [Bacon BR et al. *N Engl J Med* 2011; McHutchison JG et al. *New Engl J Med* 2010]. However, despite these overall impressive improvements in SVR rates with the PI combinations, there are still difficult-to-cure patient populations such as African Americans, patients with cirrhosis, and partial and null responders to prior PegIFN + RBV therapy. The other issue of concern is treatment-emergent resistance, which is associated with prior nonresponse or poor response to PegIFN+RBV, subtype (1a is more resistant than 1b), absence of ribavirin, and initial high viral loads. However, over time resistance variants disappear and are replaced by wild-type virus in about 0.8 to 10.0 months [Sullivan JC. EASL 2011].

New drugs for HCV continue to be identified and tested; the field of HCV therapy is expected to significantly change in the years to come. Triple therapy with response-guided duration is the new standard of care. The future will bring new triple and quad therapies, and the possibility of IFN-free regimens. New classes of drugs that include more potent second generation PIs, polymerase inhibitors, and NS5A inhibitors as well as host-targeted agents, such as cyclophilin inhibitors, are being tested.

In the ASPIRE study a PI, TMC435, added to PegIFN+RBV resulted in higher SVR rates in relapsers, partial responders, and null responders compared with placebo+RBV treated patients (Figure 1) [Zeuzem S. EASL 2012]. NS5A inhibitors offer potent antiviral activity, an average side effect profile, variable genotype coverage, and a low-to-average barrier to resistance. Daclatasvir+RBV produced significantly higher SVR rates at all doses compared with placebo+RBV in treatment-naïve genotype 1 patients. With nucleoside polymerase inhibitors+RBV, which has demonstrated a high barrier to resistance and pangenotypic activity in treatment-naïve genotype 1 patients, achieved SVR rates as high as 92%. Quad therapy may reduce resistance risk, improve potency, offer shorter duration of treatment, and offer advantages in difficult-to-cure populations.

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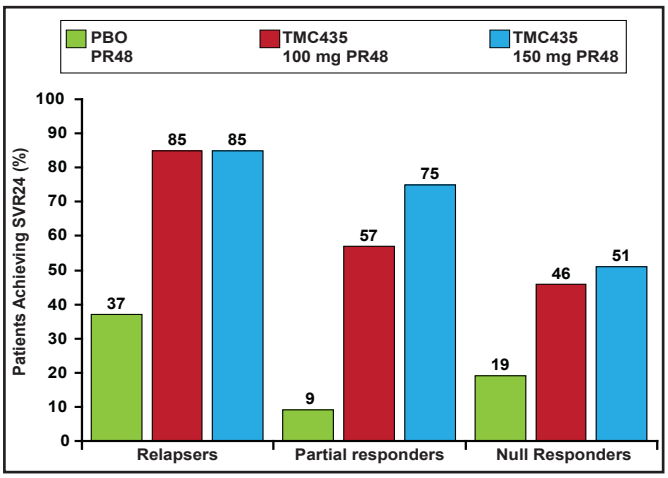
Figure 1. ASPIRE Study: TMC435 plus RBV in Genotype Treatment-Experienced.



RBV=ribavirin; SVR=sustained virologic response; PBO=placebo.

Dr. Terrault noted that although SVR rates have improved with the use of PI-triple therapy, there is still a need for better drug therapies, especially in difficult-to-cure populations, in which SVR rates are still ≤50%. Additionally, current PI-triple therapy has limited genotype coverage, requires long (48-week) treatment duration in some patients, is associated with frequent side effects, has drug-drug interactions, and has resistance issues. The next generation of triple or quad therapies is expected to have higher SVR rates, a shorter duration of therapy, broader genotype application, and simpler regimens. Deciding whether to treat now or wait for future therapies depends on the likelihood of response and risk of waiting, tolerability of PegIFN + RBV, and practical issues such as insurance status and home/work support.

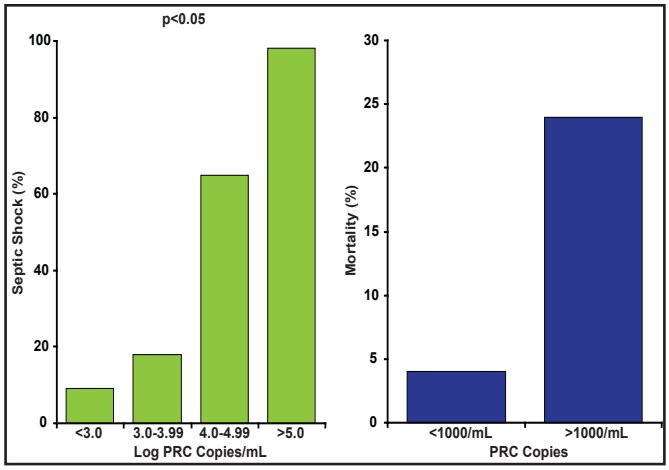
Combination Antibiotics and Outcome of Life-Threatening Bacterial Infections and Septic Shock

Written by Phil Vinall

Untreated septic shock is usually fatal within 24 to 36 hours. Clinical trials with anti-inflammatory agents in patients with sepsis are based on the assumption that the pathogenesis of sepsis is primarily driven by excessive proinflammatory activity of the cytokine network even though the triggering infection may have been eliminated by appropriate antimicrobial therapy [van der Poll T, van Deventer SJ. *Infect Dis Clin North Am* 1999]. Anand Kumar, MD, University of Manitoba, Winnipeg, Canada, suggested that the failure of these trials to show clinical benefit, in conjunction with recent experimental data, raises doubt about the validity of this assumption.

In patients with pneumococcal pneumonia, bacterial load is associated with the likelihood of death and the risk of septic shock [Rello J et al. *Chest* 2009]. As the log PCR copies of the organism go up, so does the probability of septic shock and death (Figure 1). Many studies have shown that time to antimicrobial therapy is a critical determinant of survival in meningococcal sepsis. However, when the relative impact of blood bacterial load and time to antimicrobial therapy on mortality in patients with meningococcal sepsis is considered, the critical factor is blood bacterial load. This suggests that delays in antimicrobial treatment simply mark the development of a greater bacterial load with delays in therapy and that bacterial load is the key driver of sepsis [Lala HM et al. *J Infect* 2007]. Prof. Kumar suggested that the speed of clearance of the microbial pathogen is the critical determinant of outcome in septic shock.

Figure 1. Pneumococcal Pneumonia and Risk of Septic Shock.



Reprinted with permission from the American College of Chest Physicians. Rello J. Severity of pneumococcal pneumonia associated with genomil bacteria load. *Chest* 2009; 136(3): 832.

What then is the best approach for treatment? Prof. Kumar believes that early appropriate antimicrobial therapy is the simplest effective approach and has shown that early therapy is associated with significant improvement in mortality rates across a variety of clinical infections and microbes [Kumar A et al. *Crit Care Med* 2006]. "But what can you do if you miss the early window of opportunity?" asked Prof. Kumar. One option is to increase the intensity of the therapy by using a cidal versus static drug or increasing the dose to speed elimination of the pathogen.