Ledipasvir-sofosbuvir for hepatitis C genotype 4 infection

In The Lancet Infectious Diseases, Anita Kohli and colleagues report the results of a single-centre, open-label cohort, phase 2a trial of a ledipasvir plus sofosbuvir fixed-dose combination (FDC) for adult patients with genotype 4 hepatitis C virus (HCV). The primary endpoint was the proportion of patients achieving a sustained viral response at 12 weeks after the termination of study drugs (SVR12). They enrolled 21 patients, including 13 [62%] who were treatment naive and eight [38%] who were interferon treatment-experienced, to receive ledipasvir plus sofosbuvir for 12 weeks. Patients previously treated with a direct acting antiviral, patients with decompensated cirrhosis, and patients with co-infections (eg, HIV or hepatitis B virus) were excluded. Most patients (12 [57%] of 21 individuals) had early stage fibrosis (F0–F2), with only a third of patients (seven of 21 individuals) having compensated cirrhosis. SVR12 was achieved by 95% of patients (95% CI 76–100). The only patient who did not achieve SVR12 was deemed to have a sustained virological relapse (F0–F1) at week 12. The data from their trial fits with this pattern. However, self-administration of a medication is approached cautiously by regulatory authorities, after long-term safety has been established over years of marketing. In a pandemic with a highly lethal influenza virus, this cautious approach might be re-assessed, but there is a long road ahead.

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be non-compliant. The safety profile of the FDC in this study is similar to those seen in studies of patients with HCV genotype 1. Viral clearance was rapidly reduced in these patients, with 95% having undetectable HCV RNA by week 4 of treatment according to the Roche assay (with a lower limit of quantification of 43 IU/mL). However, guidelines recommend a lower limit of quantification of 25 IU/mL or lower; thus, based on this study, 71% of patients achieved the lower limit of quantification of less than 12 IU/mL. These results in patients with HCV genotype 4 are promising in view of the efficacy and safety data.

Although this is a proof-of-concept study with a high proportion of patients achieving SVR12, the results of the study have restricted applicability. The population studied was mostly treatment-naive patients with early fibrosis (F0–2). The highest priority patients, those with advanced fibrosis or compensated cirrhosis (F3 and F4), were represented by 43% of patients in the study, and patients with co-infections were excluded. Additionally, the investigators used a Fibrosure test plus aspartate aminotransferase-to-platelet to assess fibrosis; however, there are substantial limitations in this approach. One major limitation is its lower specificity in the differentiation of F0–1 from F2. Therefore, the investigators grouped these patients together as F0–2. Reporting of the number of patients with mild fibrosis (F1) and moderate fibrosis (F2) would have been beneficial. Additionally, genotyping for the IL28B polymorphism was not done. A previous study, which contained 182 patients with HCV genotype 4 who were treatment naive, examined the predictive value of IL28B polymorphisms and treatment outcomes—ie, SVR. Patients were treated with pegylated interferon and ribavirin for 48 weeks and the patient population included patients with fibrosis stage 0–2 (55%) and 3–4 (45%), in accordance with the Metavir scoring system. The results of this study showed that IL28B polymorphisms strongly predict virological response in patients with HCV genotype 4. IL28B genotyping would have been useful data to collect, although polymorphisms probably would not have affected the results.

Existing recommendations for treatment of HCV genotype 4 include the ledipasvir plus sofosbuvir FDC for 12 weeks based on the preliminary data from this trial; the combination of paritaprevir, ritonavir, or ombitasvir with ribavirin for 12 weeks based on preliminary results of the PEARL-I trial; or sofosbuvir plus ribavirin for 24 weeks based on several other studies. The proportion of patients achieving SVR12 in the PEARL-I trial was higher in the group treated with ribavirin (100%) than in the group without ribavirin (90%), which suggests that ribavirin should be added to the regimen. The studies of sofosbuvir plus ribavirin showed that 24 weeks of treatment led to increased numbers of patients achieving SVR12 (92–100%) compared with 12 weeks of treatment (79–84%); therefore suggesting that 24 weeks of treatment should be used. These results are similar to those of Kohli and colleagues’ study, with overall SVR between 92–100%.

The advantages of treatment with the ledipasvir plus sofosbuvir FDC for patients with HCV genotype 4 compared with other recommended regimens include the short treatment duration (12 weeks), simple dosing (one pill per day), and the fact that ribavirin is not needed. Further studies of the ledipasvir plus sofosbuvir FDC for patients with HCV genotype 4 should include patients with co-infections, increased numbers of patients with advanced disease (Metavir scores of F3 or F4), and transplant patients.

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Community-acquired pneumonia is the leading cause of infectious death in USA and throughout the world. Delay in appropriate antibiotic therapy is associated with increased mortality in community-acquired pneumonia, and complications of community-acquired pneumonia such as septic shock, acute respiratory distress syndrome, and acute kidney injury. The improvements in mortality rates reported over the past decade for each of these infection-related organ failure syndromes might be substantially related to increasing emphasis on rapid provision of appropriate antibiotics.

Despite early appropriate antibiotic treatment, patients with community-acquired pneumonia still die. To further reduce the community-acquired-pneumonia mortality rate, an understanding is needed of the risks of death in patients with adequate resuscitation and early appropriate antibiotics. In The Lancet Infectious Diseases, Yuichiro Shindo and colleagues present an analysis of risk factors for mortality in patients with community-acquired pneumonia who received appropriate initial empirical antibiotics. Five risk factors were associated with mortality in these patients: albumin of less than 30 mg/L, non-ambulatory status, pH of less than 7.35, respiratory rate of at least 30 breaths per min, and blood urea nitrogen of at least 7.14 nmol/L. None of these risk factors is particularly surprising; all have been identified in previous studies of risk of either mortality or need for intensive care unit admission.

The goal of Shindo and colleagues was to develop a predictive score for use in clinical trials of immunomodulatory drugs. In these patients with community-acquired pneumonia, the need for additional interventions seems justified. The investigators propose a predictive rule based on summing the number of risk factors, justifying the score by the finding that the odds ratios of the five risk factors in multivariate analysis were similar—logical from a purely statistical standpoint.

However, the clinical impression is that community-acquired pneumonia deaths occur in a roughly bimodal distribution: young, generally previously healthy patients with overwhelming septic shock and multiorgan failure or elderly patients with several underlying chronic comorbidities. In these elderly patients, limitations on interventions are an important contributor to mortality. Unfortunately, simply recording do-not-resuscitate status does not completely capture these decisions. Some patients and families restrict interventions at the time of admission, others only after initial attempts at aggressive treatment fail, and others only minutes to hours before death.

This type of bimodal distribution is a problem for multivariate analysis, less so for predicting mortality but a major issue when the intention is risk stratification for interventional studies, the purported intent of Shindo and colleagues. The problem is true for another score derived by multivariate analysis of mortality: the Pneumonia Severity Index (PSI). This index is a good predictor of overall mortality but poor predictor of need for interventions.

Figure: Risk stratification for mortality in patients with community-acquired pneumonia receiving initially appropriate antibiotic therapy based on the classification and regression tree analysis.