C-WORTHY: the beginning of the rise of elbasvir and grazoprevir for the treatment of hepatitis C genotype 1 mono and HIV co-infected patients

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Hepatitis C virus (HCV) is one of the most common blood borne pathogens in the world. Recent studies estimate that the worldwide prevalence of anti-HCV is 115 million (1.6%), of which 80 million are thought to be viremic (1.1%) (1). Based on data from the National Health and Nutrition Examination Survey (NHANES), prevalence in the United States is reported to be 2.7–3.9 million, though the likely true prevalence of chronic HCV infection is closer to 5–7 million (2,3). Chronic HCV infection is the leading cause of end stage liver disease, hepatocellular carcinoma (HCC) and liver transplantation in the United States. It is also estimated that there are greater than 19,000 deaths each year from HCV related conditions in the United States and approximately 500,000 throughout the world (4,5).

HIV and HCV share similar methods of transmission and recent studies have suggested that the overall global prevalence of HIV/HCV co-infection is 6.2% (2–3 million people) (6). HIV has been demonstrated to accelerate liver fibrosis in patients co-infected with HCV through several different mechanisms; directly increasing HCV replication, augmenting HCV-induced hepatic inflammation and release of profibrogenic cytokines, increasing hepatocyte apoptosis, impairment of HCV-specific immune response, and enhanced lipopolysaccharide production (7). A recent study of HIV positive patients demonstrated that they had fibrosis measurements equal to HIV negative patients who were nearly a decade older (8). While antiretroviral treatment (ART) reduces the rate of hepatic decompensation in co-infected individuals, it does not completely abrogate the negative effect of HIV on HCV with co-infected patients still having higher rates of hepatic decompensation than mono-infected patients (9,10). Treatment of chronic HCV infection is paramount in this patient population.

Fueled by the development of direct acting antivirals (DAA), treatment for chronic HCV infection has evolved quite rapidly over the last several years. Previous treatment consisted of pegylated interferon based regimens with ribavirin. Not only did this treatment have poor SVR rates, particularly in co-infected individuals, it consisted of many adverse effects that prevented a great number of patients from completing therapy (11). DAA's directly target HCV non-structural proteins (NS3/4A, NS5A and NS5B) which are integral to the virus' life cycle. Since the release of the first generation DAA's in 2011 there has been an explosion in the number and combination of DAA's available. Clinical trials have consistently reported SVR 12 rates >95% for most patient populations, including those patients co-infected with HIV, which have been supported by recent real world data (12-14). Treatment guidelines maintained as a living document online by the collaboration of American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) are rapidly changing, however all oral DAA therapy is now the standard of care for all patient populations (15). The duration of therapy is being investigated as treatment regimens have expanded. Eight weeks of ledipasvir/sofosbuvir has equivalent SVR 12 rates when compared with a 12-week regimen in treatment naïve, non-cirrhotic, genotype 1 patients (16). Currently this is the only viable 8-week regimen for any patient population.

In their manuscript, Sulkowski *et al*. report the phase 2 results of the C-WORTHY trial examining the efficacy

of 8 or 12 weeks of grazoprevir and elbasvir with or without ribavirin in HCV mono-infected and HIV/HCV co-infected patients (17). Elbasvir is a NS5A inhibitor while grazoprevir is an inhibitor of the NS3/4A protease. In combination as a once daily pill, they provide an effective therapy for patients with chronic HCV infection. This regimen can be administered with HIV integrase inhibitors and certain nucleoside reverse transcriptase inhibitors (NRTI), and thus can be used in HIV co-infected individuals without any dose adjustment. In this open label randomized control study patients were recruited into eight parallel arms. Only mono-infected patients were eligible for the 8-week arm, while all HIV/HCV co-infected patients were treated with 12 weeks of therapy. There was no significant difference in SVR 12 rates between mono-infected and co-infected patients treated for 12 weeks. The addition of ribavirin was not associated with an increase in SVR 12 rates in either of these patient groups. Patients in the 8-week arm only had an SVR 12 rate of 80% which was significantly lower than those patients treated for 12 weeks (93–98%). This study also evaluated patients for NS3 as well as NS5A resistance associated variants (RAVs) before treatment as well as at the time of virological failure. Baseline NS3 RAVs did not make a difference in SVR 12 rates (91% *vs*. 92%), while patients with NS5A RAVs had a significantly lower SVR 12 rate when compared to those who had no NS5A RAVs at baseline (68% *vs*. 95%). Finally, the safety profile was similar in mono-infected and co-infected patients, with no patient discontinuing for an adverse event.

This was a fairly limited study. As the authors note, the patients that were recruited into the arms of this study were relatively easy to treat patients that were not cirrhotic and had no previous treatment experience. Those patients were recruited into other arms of the C-WORTHY trial. In addition, there were a small number of HIV/HCV co-infected patients in this trial with a limited list of permissible ART regimens. However, there are still several important factors that one can take away from this trial. It adds to the increasing number of well tolerated all oral DAA regimens that can be used for the treatment of chronic HCV infection. These early SVR 12 results were similar to the trials that investigated ledipasvir/sofosbuvir (97–99%) as well as paritaprevir/ritonavir/ombitasvir and dasabuvir (90–99%) in a similar patient population (18,19). The trial also adds to the growing evidence that HIV is no longer a barrier to treatment. The SVR 12 rates (87–97%) in this study were similar to the trials involving treatment of co-infected patients using ledipasvir/sofosbuvir (96%) as well as daclatasvir/sofosbuvir (97%) (14,20). These SVR 12 rates were not statistically different than the rates seen in treatment of mono-infected chronic HCV patients.

Previous phase 1 studies evaluating the pharmacokinetics of elbasvir and grazoprevir demonstrated that less than 1% of these drugs are renally excreted and dose adjustments are not needed in the setting of stage 4–5 chronic kidney disease (CKD) (21). Although CKD was an exclusion criteria for the C-WORTHY trial, the efficacy of elbasvir/grazoprevir was further investigated in patients with CKD stage 4–5 with or without hemodialysis in a phase 3 trial; C-SURFER (21). The SVR12 rates seen in this study (99%) were consistent with the SVR12 rates in the C-WORTHY trial as reported by Sulkowski *et al*. In addition the adverse events reported were similar in the two trials.

This trial also demonstrated poor SVR 12 rates of patients with baseline NS5A resistance (68% *vs*. 95%). The most common NS5A RAVs detected at time of virological failure were at positions Q30, L31 and Y93. This poor SVR12 rate in patients with NS5A resistance—particularly those listed—has since been corroborated in several integrated analyses of other phase 2 and 3 trials that investigated the efficacy of elbasvir/grazoprevir (22,23). SVR12 rates in this patient population were 86–89%, which were significantly lower than the subset of patients without any NS5A resistance (98–99%). Given these findings the new updated HCV guidelines recommend NS5A RAV resistance testing prior to treatment with elbasvir/grazoprevir in any patient with HCV genotype 1A, and if present extending the treatment to 16 weeks with the addition of ribavirin (15).

Perhaps the most important point, involves the failure of 8 weeks of treatment. As more and more well tolerated and extremely effective all oral DAA regimens are being developed, many trials are evaluating shorter durations of therapy as the next step in the evolution of chronic HCV treatment. To date only ledipasvir/sofosbuvir has been demonstrated to be equally effective for 8 weeks of treatment *vs*. 12 weeks, and that is only in a very specific subgroup of patients (genotype 1, non-cirrhotic with no previous history of treatment and no co-infection with HIV) (16). Eight weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir demonstrated a similar SVR 12 rate (84%) as was seen in this study (24). However, in both these trials, 8 weeks of treatment was significantly inferior when compared to a 12-week regimen.

Eight weeks of therapy has also been previously assessed in the co-infected population with varying results. The

ALLY-2 cohort involved patients with chronic HCV infection (genotypes 1–4) all of whom were co-infected with HIV and were treated with daclatasvir/sofosbuvir. These patients were randomized into 12-week and 8-week treatment arms. The overall SVR 12 rates in the 12-week arm (97%) were similar to mono-infected patients. However, the SVR 12 rate in the 8-week arm was only 76%, which was statistically different (14). Data from the German Hepatitis C Cohort (GECCO) involving real world treatment of co-infected patients with 8 weeks of ledipasvir/sofosbuvir was recently presented (25). SVR 12 rates in this group of patients (92%) were no different than the mono-infected cohort, suggesting that 8 weeks of therapy with ledipasvir/sofosbuvir may be a viable option in co-infected patients. The current recommendations are to treat co-infected patients with 12 weeks of therapy, given the paucity of evidence for 8 weeks of therapy in this patient population. The article by Sulkowski *et al*. reinforces that a minimum of 12 weeks is needed to achieve high SVR 12 rates in most patient populations.

In summary, Sulkowski *et al*. present data from C-WORTHY, a phase 2 trial examining the efficacy of 8 or 12 weeks of elbasvir/grazoprevir with or without ribavirin in mono-infected and HIV/HCV co-infected patients. Findings in this study have led to further investigation of this combination in phase 3 trials that enrolled a more diverse and complex patient population.

These further investigations have since confirmed the efficacy of 12 weeks of elabasvir/grazoprevir in HIV/HCV co-infected individuals. Other studies corroborated the low SVR 12 rates in patients with NS5A RAVs seen in this trial, and the AASLD/IDSA guidelines as well as the FDA label suggest extending therapy to 16 weeks with ribavirin in this set of patients. This early phase 2 trial laid the groundwork for elbasvir/grazoprevir's use in genotype 1 mono and co-infected individuals.

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Footnote

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Comment on: Sulkowski M, Hezode C, Gerstoft J, *et al*. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2015;385:1087-97.

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