Emerging complexities with HCV DAA regimens: Less is still *way* more.

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The arrival of interferon-free direct acting antiviral (DAA) regimens for the treatment of hepatitis C virus (HCV) infection have been transformative. Treatment approaches which were once marred by frequent and potentially severe side effects, lack of patient and provider acceptance and marginal efficacy have been replaced by DAA regimens which can cure the vast majority of patients in 12 weeks with minimal to no side effects. Despite these tremendous advances in HCV therapy providers must recognize, as with any medication, that severe side effects and medical contraindications still exist for certain populations when using current DAA therapies.

It is widely recognized that phase 3 trials can provide robust data on efficacy and general safety when studying new drugs, however, these trials are not of adequate size to identify rare adverse events.[1] This may be even more pertinent in HCV drug development trials where the results are so robust that even relatively small phase 3 studies leave little doubt with regards to efficacy and common adverse event rates.[2–5] Additionally, clinical trial populations are often more limited in the presence of comorbidities and concomitant medications than the populations these medications are likely to be used in once approved. This fact combined with limitations of pre-clinical drug interaction and animal based toxicity models create a situation in which rare side effects specific to unique drug interactions may go unidentified prior to regulatory approval.

A notable case of post-regulatory approval identification of such an adverse event is the occurrence of severe bradycardia in patients treated with sofosbuvir-containing regimens who are also on amiodarone.[6,7] Features of this interaction includes the rapid onset of bradycardia, within the first week and even after the first day of sofosbuvir, the need for at least temporary pacing, and recurrence with re-challenge if done prior to an adequate wash-out period for amiodarone. In additional pharmacovigilance data provided by the manufacturer, nine cases had been reported world-wide through 2015.[8] Both FDA and EMEA have issued warnings against the co-administration of sofosbuvir containing DAA regimens in patient also taking amiodarone.[9,10] In addition, the prescribing information for sofosbuvir and all sofosbuvir containing fixed dose combinations as well as other HCV DAAs commonly prescribed with sofosbuvir have been updated to warn to against co-administration with amiodarone.

In this issue of *Hepatology* Regan and colleagues provide in vivo animal model data supporting an interaction between sofosbuvir and amiodarone resulting in bradycardia.[11] The bradycardic effect was produced in both guinea pig and rhesus macaque experiments; data from guinea pigs further suggested the mechanism involves effects on both the sinoatrial and atrioventricular nodes with significant increases in sinoatrial node refractory time and extension of the AV node refractory period leading to some degree of AV conduction block. Strengths of their methods and observations include the use of two different in vivo animal model systems producing similar effects, careful consideration and use of physiologic concentration of sofosbuvir and amiodarone with vehicle controls, and elimination of a purely pharmacokinetic interaction by measuring intra-cardiac cellular concentrations of sofosbuvir and amiodarone. The major limitation of the current study is that, while it points us in the right direction to search for a specific mechanism (nodal automaticity and extracellular Ca^{+2} handling), one is not provided in the current set of experiments. These data convincingly reproduce the adverse reactions seen in humans.

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Perhaps most intriguing from these studies was the fact that a similar effect was not seen with MK-3682, a different pro-drug NS5B nucleotide polymerase inhibitor, suggesting that this is not a class effects. Also, in contrast to a recent abstract presentation,[12] no additional impact was found when an NS5A inhibitor was evaluated in combination with amiodarone. Explanations for this apparent discrepancy include differences in the models used to study the interaction (ex vivo perfused guinea pig heart model vs in vivo study in guinea pigs) and the use of supra-physiologic concentrations of daclatasvir in ex vivo heart model.

Of course sofosbuvir is not alone. Over the past year additional complexities have arisen for other DAA regimens approved for the treatment of chronic HCV infection. Reports of hepatic injury, including liver failure and death, in patients with cirrhosis treated with the regimen of paritaprevir/ritonavir/ombitasvir plus dasabuvir have resulted in new warning being issued with regard to the use of this regimen in patients with cirrhosis.[13] This regimen is now contraindicated in those with decompensated cirrhosis (CTP B or C). Further, enhanced monitoring of any patient with cirrhosis being treated with any HCV protease inhibitor containing regimen is now recommended.[14]

Other management complexities have also crept in to current approaches for treating HCV. A low gastric pH is required for optimal absorption of both ledipasvir and velpatasivr; a report from the HCV TARGET cohort found that proton pump inhibitor (PPI) use was associated with reduced effectiveness of sofosbuvir/ledipasvir treatment.[15] While a second report from the TRIO network did not find the same effect (a suggestion of an effect with twice daily PPIs was still seen),[16] our approach is to discontinue proton pump inhibitors, unless absolutely necessary prior to HCV therapy. If they are continued, providers must counsel patients on the proper way to take PPIs with HCV therapy. Given these interactions it is critical that providers carefully scrutinize all concomitant medication, particularly those obtained over the counter, including any herbal medications/supplements, when evaluating patients for HCV therapy. Given that we now have multiple effective treatment regimens for all genotypes, the optimal regimen should be chosen for each individual patient taking into consideration medical comorbidities and all potential drug interactions.

Viral resistance is another factor which must now be accounted for in certain situations and is unique to DAA-based HCV treatment. The presence of specific NS5A resistant variants is associated with a large decrease in SVR rates in genotype 1a patients treated with the elbasvir/grazoprevir regimen for 12 weeks without ribavirin.[17] Upon approval in January 2016, the FDA and treatment guidelines endorsed baseline resistance testing in this population prior to embarking on a treatment course with this regimen.[14] Data also suggest an impact of baseline NS5A resistance in select patient populations treated with sofosbuvir/ledipasvir, particularly treatment experienced patient who are treated for shorter durations without ribavirin.[18] Finally, current treatment guidelines recommend resistance testing in certain genotype 3 infected patient populations, primarily those with cirrhosis, prior to treatment with either sofosbuvir/velpatasvir or sofosbuvir plus daclatasvir.[14]

With many different treatment options, the ability to find an optimal treatment regimen for each patient is a reality. However, the high cost of DAA regimens has led to variable insurance requirements and restrictions; obtaining coverage for these medications can be one of the most complex management issues. Due to pricing negotiations insurances may have preferred regimens, and if the preferred regimen is not optimal for the patient, it may take significant time and logistics to argue for the more appropriate treatment. Insurance coverage varies from state to state, and despite safe and effective regimens, some insurance plans still restrict coverage of DAA treatment to patients with advanced fibrosis. In addition, authorizations may expire unknowingly or plans may require reauthorization of medications in the middle of treatment, potentially leading to treatment interruptions and impacts on efficacy.

Despite the emergence of all these "complexities" current DAA-based HCV treatment regimens remain light years ahead of HCV therapeutic approaches used less than 5 years ago, both in terms of complexity as well as safety and efficacy. The sofosbuvir-amiodarone interaction does not change the fact that DAA regimens have been transformative for HCV therapy worldwide. In practice this specific interaction impacts a very small percentage of patients, yet at the same time, highlights the vigilance needed by providers and the role they can play in identifying new side effects and complication through post-marketing experience. Practitioners must continue utilize the reporting and pharmacovigilance mechanisms available to them through the FDA (http://www.fda.gov/Safety/MedWatch/default.htm), EMA (http://www.adrreports.eu/) or other local agencies as appropriate.

While we are not quite to the point of one HCV therapeutic approach for all patients with no pre-treatment considerations, the fact remains that less is indeed way more with our current HCV therapeutic arsenal.

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