Resistance testing for the treatment of chronic hepatitis C with direct acting antivirals: when and for how long?

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Abstract

The need to test for resistance associated substitutions (RAS) has been intensively debated in the past two years. In the absence of pangenotypic combinations, it seems reasonable that, if available, RAS testing in the NS5A gene at baseline for genotypes 1a and 3 may help to avoid overtreatment in terms of ribavirin usage and/or prolonged treatment duration. When patients fail treatment, RAS testing may also be useful to guide the selection of the new regimen, especially for those that need urgent retreatment and that have failed a combination including an NS5A inhibitor. However, there are new drugs in the pipeline that in combination are pangenotypic, very potent and with a high genetic barrier to resistance. In this new scenario, RAS testing may not play such an important role.

Keywords: HCV, RAS, DAA, baseline, failure, new drugs

The key to achieve sustained viral response (SVR) in the treatment of chronic hepatitis C with direct acting antivirals (DAAs) is to eliminate all the hepatitis C virus (HCV) quasispecies that infect the patient; if this is achieved, and the entire viral population has been eradicated, there is no opportunity for viral relapse and the patient is cured of HCV

infection. Achieving SVR is a multifactorial event relying not only on virological factors, but also on factors related to the host and the drugs used for treating chronic hepatitis C.¹ Being infected by genotypes 1a or 3, cirrhotic, and previously exposed to interferon-containing regimens are predictors of non-response. Among other virological factors that may impact SVR, the presence of resistance associated substitutions (RAS) may be clinically relevant, both before the patient is going to start the first DAA regimen and when the patient has failed treatment.

Although phenotypic tests may be performed to assess resistance to DAAs, genotyping (e.g. sequencing of the HCV genomic region of interest) is considered the gold standard to detect RASs. Next generation sequencing is now available for DNA sequencing and many laboratories have adopted this technology; however, unlike other scenarios, next generation sequencing has not been proven clinically relevant for HCV RASs testing; in fact, the detection of RASs present with a low relative frequency in the quasispecies viral population, below a 15% cutoff, failed to demonstrate any impact on SVR.^{2,3} In addition, to score resistance in HCV, the type of RAS is also critical, especially for the NS5A inhibitors, where class RASs (all substitutions in NS5A with a fold-change (FC) greater than 2.5X to any drug in the class) do not necessarily have the same impact as

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drug specific RASs (specific RASs for each drug in the class, in general with FC values above 100X).

The need to test for RASs at baseline has been highly debated through the last two years. In general, expert opinion at major conferences has always been that baseline RAS testing has no or a minimum impact on SVR, and therefore baseline RAS testing was not needed for clinical practice. However, clinical guidelines from the American Association for the Study of Liver Diseases⁴ (AASLD) recommend testing for Q80K in genotype 1a prior to using simeprevir in interferon-containing regimens, and more recently in cirrhotic patients that are going to start sofosbuvir (SOF) and simeprevir (SIM). For NS5A inhibitors, AASLD guidelines recommend to test for RASs in NS5A if the combination grazoprevir (GZR) and elbasvir (EBR) is going to be used, as the detection of clinically relevant RASs against EBR will aid to decide if prolonging treatment to 16 weeks and adding ribavirin (RBV) is necessary. For other regimens, such as the AbbVie combination (paritaprevir/r-dasabuvir-ombitasvir, known as 3D) RAS testing is not necessary as there is no impact for HCV genotype 1b treatment, as there also isn't for all the other DAA combinations and genotype 1b.

For genotype 1a, the 3D approved regimen always includes RBV to make the regimen more potent and overcome the effect of RASs. Guidelines from the European Association for the Study of Liver diseases⁵ (EASL) have been updated September 2016; EASL panel state that if RAS testing is accessible, reliable and interpretable, then testing for baseline RAS for HCV genotypes 1a, 4, 5 and 6 will help to decide on extending treatment duration and adding RBV for any of the SOF and ledipasvir (LDV), SOF and daclatasvir (DCV) combinations, and as AASLD for GZR/EBR for genotype 1a. Very recently, Zeuzem et al.³ clearly showed that HCV genotype 1a infected patients starting SOF/LDV with LDV specific RASs (15% cutoff) and prior interferon treatment experience, irrespective of the cirrhosis status, and those interferon-naïve with cirrhosis, are prone to achieve lower SVR rates when compared to HCV genotype 1b infected patients or treatment-naïve non cirrhotic genotype 1a, who achieve SVR rates of 96-98%. Results for treatment-naïve and treatment-experienced genotype 1 infected patients, with and without liver cirrhosis are illustrated in Figure 1.

HCV genotype 3 is also difficult to treat with currently available DAAs. NS5A baseline RAS, especially Y93H, may condition lower SVR12

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Figure 1. SVR12 rates achieved considering LDV specific RAS and a 15% cutoff. Data are presented in relation to prior interferon treatment (TN=treatment naïve; TE= treatment experienced), and cirrhosis status (C=cirrhosis; NC=non cirrhosis)

Table 1. New drug combinations that have demonstrated high SVR rates in patients who have failed a prior course of interferon free DAA regimen

Drugs	Study population	Study
SOF/VEL/VOX	12 weeks for NS5A inhibitor-experienced GT1-6 HCV	POLARIS-1 ¹⁵
SOF/VEL/VOX	12 weeks for DAA-experienced (no NS5A inhibitors) GT1-6 HCV	POLARIS-4 ¹⁶
GLE/PIB	12 or 16 weeks for patients with GT3 HCV ± treatment experience ± cirrhosis	SURVEYOR-II/3 ¹⁷
MK-3682/GZR/RZR	16 weeks + RBV for 8-week MK-3682/GZR/(RZR or EBR) failures	C-CREST Part C ¹⁸
MK-3682/GZR/RZR	16 or 24 weeks ± RBV for GT1 HCV patients relapsing on DAAs	C-SURGE ¹⁹

HCV – hepatitis C virus; EBR – elbasvir; GLE – glecaprevir; GT – genotype; GZR – grazoprevir; PIB – pibrentasvir; RBV – ribavirin; RZR – ruzasvir; SOF – sofosbuvir; VEL – velpatasvir; VOX – voxilaprevir.

rates (75%) when starting SOF/DCV in real life conditions.⁶ Data from the ASTRAL 3 study,⁷ where SOF and velpatasvir (VEL) were used for the treatment of genotype 3 infected patients, have also shown the impact on SVR12 of the Y93H RAS in NS5A (88%). In fact, AASLD guidelines recommend testing for Y93H before genotype 3a cirrhotic patients start any SOF/NS5A inhibitor combination, to decide whether extending treatment duration and adding RBV may be necessary.

Regarding patients that have failed a prior DAA regimen, and that are in urgent need of retreatment, there is a general consensus that RAS testing provides added value for clinical practice. Lawitz et al.⁸ addressed the retreatment with SOF/LDV and RBV for 24 weeks in patients that had failed a previous course of SOF/LDV for 8-12 weeks ± RBV; although only 41 patients were studied, the results showed a clear impact of the number and the type of RAS in NS5A on SVR12: patients that had no RASs at failure achieved 100% SVR12 rates when they were retreated with the same regimen they had failed, but with a 24 week duration and with RBV. Some other trials such as QUARTZ-I⁹ and CSWIFT-retreatment¹⁰ have also addressed the retreatment of patients failing the 3D regimen or GZR/EBV with the addition of SOF and RBV, with excellent results. Real-life studies have also addressed the importance of resistance testing for the retreatment of patients who have failed a first line DAA therapy: Vermehren et al.¹¹ showed excellent results in a German real life cohort

when retreatment was resistance-guided; in a similar way, Cento et al.¹² and Perez et al.¹³ also show data on resistance-guided retreatment of first line DAA failures in large Italian and Spanish cohorts, respectively.

Although resistance has been proven to play a role on both initial treatment and retreatment, there are some important caveats for the introduction of resistance testing in clinical practice that need to be highlighted. As EASL guidelines underline, the test needs to be reliable and interpretable. Reliability is certainly an issue, and only accredited laboratories with sufficient expertise both on technical issues on DNA sequencing and HCV RAS interpretation should provide results. Variability of interpretation is also important, as no clinically validated rules of interpretation are available so far. Although the Lontok et al. consensus¹⁴ on HCV interpretation may help for a uniform interpretation of the results, the document is now outdated, as new drugs that are currently available, and new RASs that have been described, are not in the text. Several actions aiming to provide guidance on sequencing methods and RAS interpretation are currently being evaluated for publication in high impact HCV journals and will soon be available for public use. Hopefully, these guidance documents may help to make resistance testing for HCV more reliable and interpretable, and will certainly contribute to improve access to resistance testing in many settings.

New combinations of drugs, including very potent and pangenotypic drugs, such as

voxilaprevir (VOX), glecaprevir (GLE), pibrentasvir (PIB), ruzasvir (RZR), uprifosbuvir (MK-3682), are currently in different phases of drug development and have entered phase II/III clinical trials. Some of these combinations are proving to be extremely efficacious for the treatment of interferon treatment-experienced, cirrhotic patients infected with the difficult to treat genotypes 1a and 3, and have already shown excellent SVR rates for treating patients that have also failed interferon free DAA containing regimens (Table 1). Presumably, when these combinations become available, RAS testing may not play an important role for clinical practice. However, we do not know yet how these drugs will be used, and how will they be rolled-out across different countries. In the meantime, until they are here, there is a clear role of RAS testing in the clinical practice, and a need to improve access to reliable testing and interpretation. HCV infected patients will certainly benefit from it.

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