Resistance to direct antiviral agents for hepatitis C virus infection. Impact on clinical practice?

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Editors

Since the first generation protease inhibitors boceprevir & telaprevir were approved in combination therapy with peginterferon & ribavirin, we live in a time of outstanding revolution in hepatitis C virus infection. For many of us, this may be the first opportunity to see how an infectious disease agent was discovered and, also, how it may be eradicated. The opportunity to cure HCV infection became real when HCV life cycle was described, and viral targets for HCV direct antiviral agents (DAA) were identified. Protease inhibitors, first, followed by the high genetic barrier NS5B inhibitor sofosbuvir and the highly potent NS5A inhibitors, used in combination, have made possible to achieve cure rates that only 5 years ago were unthinkable. Today, different HCV genotypes can be treated with cure rates, measured as sustained viral response (SVR), greater than 90-95%. However, as many patients are being treated, a small percentage of failing patients may result in a high number of patients for which a re-treatment regimen will be needed. For instance, if 100.000 patients have access to treatment in a given country, as many as 5.000 patients may not achieve SVR, and may need to go onto a second treatment line to achieve a cure.

So, do we have tools to predict, or to avoid treatment failure? And, once the patient has failed, can we know which would be the best regimen we can use for retreatment? From a virological perspective, resistance associated substitutions (RASs) may play a role for both scenarios, though this is highly debated and controversial.

For initial treatment the discussion is whether RASs may help or not to choose which regimen should be avoided; to properly address this issue, some other factors must be considered: a) the viral genotype, b) if the patient has been treated previously with an interferon containing regimen, c) if the patient is or not cirrhotic, d) for how long is the patient going to be treated, and e) if ribavirin will be added. For this multifactorial setting, it seems clear that for cirrhotic patients, infected with genotypes 1a and 3, and/or with prior treatment experience with IFN, RASs detection in NS5A helps to achieve higher cure rates when a NS5A inhibitor is in the DAA regimen, as it will help to personalize the treatment and decide on treatment duration and addition of ribavirin. For those scenarios in which RASs detection may not be available, to be on the safe side, the longest duration and adding ribavirin may be the best option, but indeed this is going to result in the overtreatment of many patients, as RASs in NS5A are not very prevalent.

For patients that have failed a first line of IFN-free DAA regimen, RASs detection may help on the decision on which regimen will be the best option for the patient. Although few, some cohorts running, mainly in Europe (Germany,¹ Italy² and Spain³) have partially (as they are real life studies that are still in progression) addressed this issue. Some very potent DAA combinations with new drugs (voxilaprevir, glecaprevir,

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pribentasvir, ruzasvir and MK-3682) are in late stage of development and will soon be available for clinical practice. As these drugs in different combinations may be suitable for overcoming resistance, for those patients that do not need to be retreated urgently, waiting for the arrival of these new drugs may be the best option, especially for those with a complex pattern of RASs at failure.

In summary, though it may seem that resistance may not play a role for clinical management of HCV treatment, for those difficult-to-treat patients, if we want to adhere to the “when you treat first, treat well” principle, RASs detection will help to individualize treatment and avoid failure. In addition, until new drug combinations are available, RAS detection in those patients that fail to achieve

SVR will also be of help for clinical decisions on which will be the best strategy to effectively cure the patient.

Conflicts of interest: none to declare.

References

1. Vermehren J, Susser S, Dietz J, et al. Retreatment of patients who failed DAA combination therapies: Real-world experience from a large hepatitis C cohort. EASL Conference 2016, Barcelona, April 2016; Abstract PS103.
2. Di Maio VC, Cento V, Lenci I, et al. Virological failures to direct acting antivirals (DAA) regimens in a real life setting show frequent resistance associated variants and may require re-treatment with unconventional strategies. AASLD Conference, Boston, November 2016; Abstract 1944.
3. Perez AB, Chueca N, Fernandez-Caballero JA, et al. Patients failing all-oral interferon-free DAA regimens in Spain. Virological characterization of the HCVREsp cohort. AASLD Conference, Boston, November 2016; Abstract 1471.

Please cite this article as:

Pérez AB, García F. Resistance to direct antiviral agents for hepatitis C virus infection. Impact on clinical practice? GERMS 2016;6(4):123-124. doi: 10.11599/germs.2016.1098