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REVIEW

Resistance to hepatitis C virus. Implications and therapeutic options☆

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Abstract We are currently living in an unprecedented era of hepatitis C treatment with the availability of highly effective drugs yielding minimal side effects. The problem we currently face is the retreatment of patients refractory to these drugs. Although several factors can influence treatment failure, this review focuses on antiviral resistance. Resistance-associated substitutions may be identified at baseline or be treatment-emergent. The latter seem to be more clinically relevant and must be studied in the event of treatment failure (no virological response). In this article, we present the latest data from clinical trials and studies in real-life clinical practice. Finally, based on this current evidence, we propose some recommendations for the management and retreatment of these patients.

PALABRAS CLAVE
Virus de la hepatitis C;
Agentes antivirales directos;
Resistencia viral;
Fallos a tratamiento;
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Resistencias al virus de la hepatitis C. Implicaciones y posibilidades terapéuticas

Resumen En el momento histórico en el que nos encontramos en el ámbito del tratamiento de la hepatitis C, en que disponemos de fármacos excepcionalmente eficaces y con muy escasos efectos secundarios, se nos plantea el problema del retratamiento en los pacientes que fracasan al mismo. Los factores que influyen en el fracaso son muy diversos, si bien en esta revisión nos vamos a centrar en las resistencias antivirales. Las sustituciones asociadas a resistencias pueden ser tanto basales como inducidas por el tratamiento; estas últimas parece que son las más importantes clínicamente y las que deben ser estudiadas ante la falta de respuesta virológica.

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En este artículo ofrecemos los últimos datos de ensayos clínicos y estudios en práctica clínica real, y en base a la evidencia actual se ofrecen unas recomendaciones de manejo y retratamiento de estos pacientes.

Introduction

Direct-acting antivirals (DAAs) are currently the treatment of choice for hepatitis C virus (HCV) infection.[1] These drugs achieve a sustained virologic response (SVR) rate of over 90% in virtually all population groups, and only slightly lower in cirrhotic patients with genotype 3 infection in whom prior treatment has failed. DAAs also present an excellent safety profile, especially in regimens that do not include ribavirin (RBV).

Therefore, it is time for us to turn our attention to therapeutic failures, which can be due to various host-, virus-, or antiviral-related factors (Fig. 1). One of the most interesting causes of treatment failure is the development of resistance-associated variants (RAVs). Accurate RAV testing is essential. Understanding of RAVs has improved remarkably, and we now know that not all are clinically significant, and not all need to be analysed.

This review aims to provide an in-depth analysis of RAVs, what they are, their clinical importance, when they appear, when to test for RAVs or not, and by what method. This analysis of RAVs will enable clinicians to select the best retreatment regimen for their patients.

Hepatitis C virus. Virological concepts and variability

HCV is a single-chain RNA virus belonging to the *Hepacivirus* genus of the *flaviviridae* family of viruses discovered in 1989.[2] HCV circulates in the blood in the form of lipoviro-particles. Once it enters the hepatocyte, the RNA is released and begins to synthesise the polyprotein that will be processed by viral (NS2-3 and NS3-4A) and host proteases. New copies of RNA are formed in the viral replication complex, which is composed of non-structural proteins (NS3, NS4A, NS4B, NS5A and NS5B). As a result, intracellular membranes are reorganised to generate an ideal viral replication micro environment called the membranous web, composed of double-membrane vesicles. Finally, assembly takes place in the endoplasmic reticulum.

HCV is an exceptionally variable virus,[3] thanks to its high estimated turnover rate of 2–5 h, and its enormous daily virion output (10^{12} virions) per patient. Added to this is its high rate of mutation (10^{-4} to $\times 10^{-5}$ per nucleotide and per replicative cycle) due to the low error-repair capacity of RNA-dependent RNA polymerase.[4,5]

This gives rise to the large number of HCV variants, most of which are directly eliminated by the immune system or are unable to replicate due to loss of coding proteins. Others, however, are able to survive and perpetuate the infection.

The variants that survive give rise to the 7 different *genotypes*, differentiated by a 30%–35% variation in nucleotide sequence, and 67 *subtypes*, whose genomic sequence varies by between 20% and 25%. In addition, a dominant species (wild type) and different *quasispecies*, with a sequence variability of up to 10%, can be found in the same patient.

Causes of therapeutic failure

Failure of antiviral treatments may appear at different times:

- During antiviral treatment, it is called breakthrough.
- Once the treatment is completed, it is called viral relapse. This is most common in patients receiving DAAs.
- Null response to antiviral treatment, primary absence of response to treatment.

As explained above, modern antivirals are extremely effective. However, 1%–7% of patients are not able to be cured.[6] This is due to many different reasons.

Before focussing on resistance-related HCV treatment failures, we will briefly explain the other reasons for therapeutic failure. These are summarised in Fig. 1.

- Patient-related causes: male gender, compensated cirrhosis, failure of previous treatments (based on interferons [IFNs] or DAAs)
- Virus-related causes: genotype 1a, 3, baseline NS5A RAVs, RAVs developed after treatment with DAAs, Q80K (only in patients receiving treatment with simeprevir [SMV]), unfavourable IL28b polymorphism.

There are other causes of virological failure aside from RAVs. These include genotyping errors, genetic recombination phenomena (rare cross-linking of RNA intermediates leading to recombination of 2 viral strains, for example, 1 hybrid virus with genotype 1 and 2), persistent infections, reinfections, superinfection (combination of reinfection and persistent infection evidenced in the phylogenetic analysis of the virus), or coinfections.

- Treatment regimen-related causes: lack of adherence to treatment, short treatments, no RBVs.

For virological failure to occur, 2 or more of the aforementioned factors must be present in the same patient,[6]