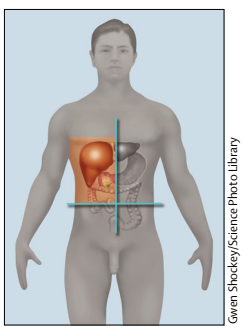
New anti-HCV drug combinations: who will benefit?



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Treatment of chronic hepatitis C has evolved rapidly. The first two direct-acting antiretroviral drugs were approved in 2011; just 2 years later the first interferon-free regimen was introduced. Now, 3 and a half years later, seven highly effective combinations of direct-acting antiretroviral drugs are available, the most recent being glecaprevir (a second-generation protease inhibitor) coformulated with pibrentasvir (a second-generation NS5A inhibitor; Maviret; Abbvie, North Chicago, IL, USA) and sofosbuvir, velpatasvir, and voxilaprevir (Vosevi; Gilead, Foster City, CA, USA). Almost all available combinations achieve cure rates close to 100% and are well tolerated. In June, 2017, Maviret was granted a positive opinion from the European Committee for Medicinal Products for Human Use for treatment of chronic HCV; In July, Vosevi was licensed by the US Food and Drug Administration and the European Medicines Agency.

In *The Lancet Infectious Diseases*[1] Xavier Forns and colleagues present the results of a phase 3 trial assessing the efficacy and safety of 12 weeks of treatment with glecaprevir (300 mg) coformulated with pibrentasvir (120 mg) in patients with chronic hepatitis C virus (HCV) genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Of 146 enrolled patients, 145 (99%, 95% CI 98–100) achieved a sustained virological response. The study did not include patients with decompensated cirrhosis; the same is true for studies of sofosbuvir, velpatasvir, and voxilaprevir.[2] In general, regimens containing protease inhibitors should not be given to patients with decompensated cirrhosis. At present, these patients should be treated with sofosbuvir combined with ledipasvir, velpatasvir, or daclatasvir.[3] Patients with HCV genotype 3a infection are more difficult to treat, with cure rates of 96% reported with glecaprevir plus pibrentasvir[4] and 89–98% with combination sofosbuvir and velpatasvir.[5] These second-generation direct-acting antiviral combinations might make treatment easier since genotype testing will no longer be needed, thus enabling them to be used even in countries with less technical expertise and experience in HCV treatment. Genotyping might not be necessary in the era of pangenotypic drugs.

However, the limitation of access to these potentially life-saving medications cannot be solved by introduction of new treatments alone. The biggest question is how these new drugs will be used. Overall, their efficacy is minimally better than that of the already available drug combinations. In patients with genotype 1b infection, treatment with ombitasvir, paritaprevir, and dasabuvir[6,7] is as effective as treatment with coformulated glecaprevir and pibrentasvir;[8] in patients without cirrhosis, even 8 weeks of treatment with ombitasvir, paritaprevir, and dasabuvir is sufficient.[9] The same is true for patients with genotype 4 infection.[10] The only relevant advantage of coformulated glecaprevir and pibrentasvir compared with ombitasvir, paritaprevir, and dasabuvir is that patients have to take three tablets instead of four. Ribavirin is not needed with coformulated glecaprevir and pibrentasvir in patients with genotype 1a infection, thus preventing ribavirin-induced side-effects.

The most commonly reimbursed treatment for chronic hepatitis C in Europe is ombitasvir, paritaprevir, and dasabuvir with or without ribavirin. Drug pricing is not transparent in Europe, but ombitasvir, paritaprevir, and dasabuvir seems to be the cheapest drug combination on the market. The price of a particular drug varies considerably among the EU member states. Usually hepatitis C drugs are most expensive in Germany and cheapest in Romania. As a hepatologist, it is not my job to recommend how to market a drug. The price will probably dictate which drug will be paid for by third-party payers. Drug prices are fixed in bazaar-like negotiations; thus, neither glecaprevir coformulated with pibrentasvir nor sofosbuvir, velpatasvir, and voxilaprevir are likely to be first-line drugs, at least outside the USA. From the prescriber side, the best solution would be that all drugs cost the same and the treater has the possibility to choose the best option for the patient. The hope is that Abbvie will not take ombitasvir, paritaprevir, and dasabuvir from the market to increase the sales of glecaprevir and pibrentasvir. The same argument can be made for the Gilead drugs.

Coformulated glecaprevir and pibrentasvir and sofosbuvir, velpatasvir, and voxilaprevir will most likely be used to treat non-response to or relapse after first-line treatment. NS5A resistance-associated substitutions are mostly responsible for treatment failure with the currently available regimens.[11] Pibrentasvir is effective against the most common NS5A resistance-associated

substitutions at positions 30, 31, and 93. None of the patients included in the EXPEDITION-1 trial had failure of a previous NS5A inhibitor-containing regimen, but 40% of those sequenced had NS5A mutations at baseline, including the one patient who relapsed at week 8 after treatment with glecaprevir and pibrentasvir.[1]

Society should be happy to have safe drugs with high efficacy for treatment of HCV. However, optimal use of these drugs will depend on them being accessible to infected patients worldwide, and receiving high priority on the political agenda.

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