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VIRAL HEPATITIS

New hepatitis C therapies—a medical pick and mix

A plethora of direct-acting antivirals (DAAs) for the treatment of hepatitis C is now available and new agents are continually being added to this list. To coincide with the International Liver Congress 2014 in London, UK, the *New England Journal of Medicine* has published a series of new HCV therapy phase III trial results, demonstrating that we are now truly in the era of interferon-free, all-oral combination therapies for HCV infection. These DAAs could potentially revolutionize treatment for hepatitis C, but can we call them a cure yet?

The first set of three open-label trials examined the use of the HCV NS5A inhibitor ledipasvir in combination with sofosbuvir (an HCV NS5B polymerase inhibitor). A number of different patient populations infected with HCV genotype 1 were studied: HCV-infected patients who were treatment-naive (16% had cirrhosis; 12-week versus 24-week regimen, with or without ribavirin); patients with chronic HCV infection without cirrhosis (8-week versus 12-week treatment regimen, with or without ribavirin); and HCV-infected patients who had failed to achieve a sustained virologic response (SVR) despite treatment with interferon-based therapies (20% had cirrhosis; 12-week versus 24-week regimen, with or without ribavirin).

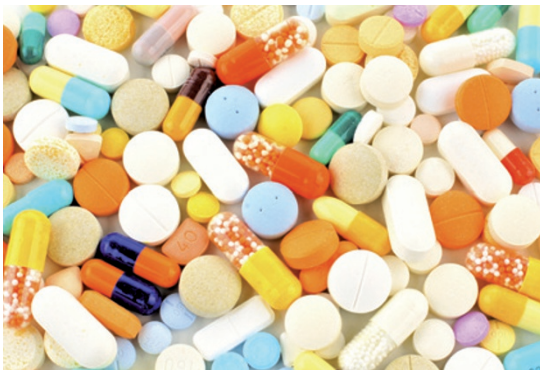
Patients typically received 90 mg ledipasvir and 400 mg sofosbuvir in a combination tablet orally each day; ribavirin, when required, was administered at 1,000 mg or 1,200 mg according to bodyweight. The studies showed that once-daily ledipasvir–sofosbuvir (with or without ribavirin) was highly effective (SVRs >90%, with some rates as high as 99%) in HCV-infected patients irrespective of whether they had received HCV treatment before. Importantly, the studies found that there was no additional benefit of including ribavirin within the combination therapy, and Kowdley *et al.* found no benefit of extension of the treatment period to 12 weeks (8 weeks were sufficient).

The second set of three trials examined the use of a three-in-one pill of ABT-450 (an HCV NS3/4A protease inhibitor), ritonavir plus ombitasvir (an HCV NS5A inhibitor) in combination with dasabuvir (a non-nucleoside NS5B polymerase inhibitor) and ribavirin. Again, a number of different patient populations infected with HCV genotype 1 were examined: previously untreated HCV-infected patients without cirrhosis (12-week, double-blind, placebo-controlled trial); HCV-infected patients with cirrhosis (12-week versus 24-week regimens); and HCV-infected patients who had been previously treated with PEG-IFN and ribavirin, including nonresponders (12-week regimen).

Patients typically received 150 mg ABT-450, 100 mg ritonavir and 25 mg ombitasvir once daily, 250 mg dasabuvir twice daily and either 1,000 or 1,200 mg ribavirin depending on bodyweight. Again, these new DAA drug combinations were highly effective, achieving SVRs >90%. In addition, the drugs seemed to be safe, with drug discontinuation owing to adverse events being infrequent.

With an estimated 170–180 million people infected with HCV worldwide, the need for effective treatment is apparent and the new DAAs are providing the clinical community with optimism. "We can say that we now have a cure for hepatitis C, which is particularly true for treatment-naive patients without advanced cirrhosis," says Professor Michael Manns, Hannover Medical School, Germany, who is not an author of the new studies. This sentiment has been echoed in new WHO guidelines for the screening, care and treatment of patients infected with HCV. However, as hepatitis C treatment rapidly evolves, Manns acknowledges that clinicians are currently working with a "moving target" when it comes to how best to treat their patients as new drugs and new drug combinations emerge. It is not just a question of which drug to use, but which combination of drugs to choose.

Despite their success, a major issue of concern with these new DAAs has been their expense, as well as regulatory issues across different countries. Hopefully, over the coming years, these therapies will follow the lead of the HIV field and substantially reduce in cost.



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Several major challenges do remain before we can truly move towards the global eradication of HCV infection, particularly access to new DAAs in low-income and middle-income countries and effective HCV screening programmes (too often diagnosis still comes at a late stage). Moreover, more attention needs to be focused on special patient populations. "We still have yet to explore treatments in patients with decompensated cirrhosis," Manns explains, "which is a major task".

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Original articles Afdhal, N. *et al.* Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N. Engl. J. Med.* doi:10.1056/NEJMoa1402454 | Kowdley, K. V. *et al.* Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N. Engl. J. Med.* doi:10.1056/NEJMoa1402355 | Afdhal, N. *et al.* Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N. Engl. J. Med.* **370**, 1483–1493 (2014) | Feld, J. J. *et al.* Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N. Engl. J. Med.* doi:10.1056/NEJMoa1315722 | Poordad, F. *et al.* ABT-450/r–ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N. Engl. J. Med.* doi:10.1056/NEJMoa1402869 | Zeuzem, S. *et al.* Retreatment with HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. *N. Engl. J. Med.* doi:10.1056/NEJMoa1401561

Further reading WHO. Guidelines for the screening, care and treatment of patients infected with hepatitis C infection. *WHO* [online], http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/