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THERAPY

Reaching for the stars — effective HCV drugs for all?

> "…it is now time to move from drug development to drug delivery"

A combination pill of sofosbuvir and velpatasvir is effective across different HCV genotypes and in different patient populations with hepatitis C, including those with compensated or decompensated cirrhosis. Reported in the *New England Journal of Medicine*, the findings by the ASTRAL-1, 2, 3 and 4 investigators point towards effective HCV treatment with broad coverage across a variety of patient groups.

HCV infection is a major public health problem worldwide. HCV treatment has been revolutionized by the new all-oral, interferon-free regimens developed in the past few years. However, despite this progress, clinical decision-making during the management of patients infected with HCV is difficult owing to the multitude of new drug regimens available and because patient and disease characteristics can vary widely (such as HCV genotype, treatment history and stage of fibrosis or cirrhosis), which can affect efficacy.

Now, three phase III clinical trials have tested the efficacy of a single-pill combination therapy of sofosbuvir (400 mg, an HCV NS5B polymerase inhibitor) and velpatasvir (100 mg, a pangenotypic HCV NS5A inhibitor). The therapy was administered orally once daily for 12 weeks in a wide variety of patients, with the primary end point of a sustained virologic response (SVR) at 12 weeks after the end of therapy.

A high SVR was achieved in all the trials using the sofosbuvir–velpatasvir regimen. In ASTRAL-1, a 99% SVR was reported in patients infected with HCV genotype 1, 2, 4, 5 or 6, including those with compensated cirrhosis, and a mix of untreated patients and those who had received prior HCV treatment. Similar high SVRs (>95%) were observed with this combination therapy in the ASTRAL-2 and ASTRAL-3 trials of individuals infected with HCV genotype 2 or 3 (with or without compensated cirrhosis and/or prior treatment).

For ASTRAL-4, overall, 83% of individuals with HCV infection (genotype 1, 2, 3, 4 or 6) and decompensated cirrhosis achieved a SVR with the combination therapy, rising to 94% with the addition of ribavirin to the regimen. "This [result] is a major advance for the treatment of patients of all genotypes with decompensated liver disease," says first author of the ASTRAL-4 trial Michael Curry. "Presently, the only treatment for patients with decompensated liver disease is liver transplantation," he explains. Adverse events were reported in all trials, the most common being headache, fatigue and nausea.

"With one regimen that is effective for all patients, there is the possibility to move HCV treatment out of specialty clinics and into primary care," says Jordan Feld (first author of the ASTRAL-1 trial), but adds there is still much to do to move the HCV therapy field from drug discovery to public health and clinical implementation.

A similar sentiment is held by Graham Foster (first author of the ASTRAL-2 and ASTRAL-3 trials) who argues that it is now time to move from drug development to drug delivery. "Going forward I think we now have the tools to develop global viral control programmes based on widespread treatment, and the next step will be to evaluate how best to deliver these medicines on a global scale," he adds.

Although new HCV drug regimens have been heralded as a 'cure', key issues need to be addressed before HCV treatment can be truly scaled up for global hepatitis C treatment programmes. Cost is a major factor for widespread implementation of these new drug regimens, but improvements in diagnosis and a better understanding of HCV transmission are also required. Moreover, efforts to develop an HCV vaccine for eradication are still ongoing.

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