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HCV Treatment — No More Room for Interferonologists?

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The landscape of therapy for hepatitis C virus (HCV) infection is changing rapidly. Until recently, the standard of care for HCV infection was a combination of peginterferon and ribavirin. Our increased understanding of the basic biology of HCV led to the identification of specific proteins involved in the replication of the virus. These proteins can be targeted by protease and polymerase inhibitors.

Two years ago, the advent of protease inhibitors, such as telaprevir and boceprevir, profoundly affected the field.[1,2] These agents improved the likelihood of cure but came with a number of inherent limitations. Protease inhibitors do not have antiviral activity in HCV genotypes other than the predominant genotype 1, which leaves at least five other HCV genotypes without coverage. Moreover, protease inhibitors can promote viral resistance, which usually signals therapeutic failure, and have multiple pharmacokinetic interactions with other drugs. Finally, protease inhibitors need to be administered with peginterferon and ribavirin, two drugs with extensive and well-established side-effect profiles that are aggravated by the addition of telaprevir or boceprevir.

Clinicians who treat patients with HCV infection have learned to accept and treat adverse effects as an integral part of patient care, but the inclusion of protease inhibitors in the therapeutic arsenal has added a layer of complexity. Indeed, the major challenge of contemporary interferon therapy is adequate management of side effects. Physicians and patients are ready for less toxic therapeutic options.

Two groups of investigators (Jacobson et al.[3] and Lawitz et al.[4]) now suggest in the *Journal* that change is about to happen. They describe the use of sofosbuvir, a novel polymerase inhibitor, in a series of four experimental studies targeting patients with HCV infection. In three randomized trials — FISSION, POSITRON, and FUSION — investigators focused on patients with HCV genotype 2 or 3, as seen in everyday clinical practice, including patients who had received no previous treatment, those who were unwilling to take interferon or had unacceptable side effects, and those who did not have a response to previous therapy. All the studies had a similar end point: a sustained virologic response at 12 weeks after the end of therapy. In addition, in the single-group, open-label NEUTRINO study, investigators studied the use of a sofosbuvir-based regimen in patients with genotype 1, 4, 5, or 6 infection.

The FISSION study examined the efficacy of 12 weeks of sofosbuvir plus ribavirin, as compared with the standard of care, peginterferon alfa-2a plus ribavirin, administered for 24 weeks. Standard therapy was successful in 78% of patients with genotype 2 infection and 63% of those with genotype 3 infection, as compared with rates of 97% and 56%, respectively, with the sofosbuvir-based regimen.

The POSITRON study evaluated a population that was not deemed to be eligible for interferon-based therapy and compared 12 weeks of sofosbuvir plus ribavirin with placebo. The primary reasons for ineligibility were a preexisting psychiatric disorder (57%) or autoimmune disorder (19%). None of the patients in the placebo group achieved the end point, but 93% of those with genotype 2 infection and 61% of those with genotype 3 infection had a sustained virologic response with sofosbuvir plus ribavirin.

The FUSION study, which targeted patients without a sustained response to interferon-based therapy, compared a 12-week regimen of sofosbuvir–ribavirin with a 16-week regimen. Four additional weeks of treatment made a difference, with an increase in the rate of sustained virologic response from 86% to 94% in patients with

genotype 2 infection and from 30% to 62% in those with genotype 3 infection.

Finally, the investigators captured some evidence for the pangenotypic anti-HCV properties of sofosbuvir. In the NEUTRINO study, patients with genotype 1 infection (89%), genotype 4 infection (9%), or genotype 5 or 6 infection (2%) who received 12 weeks of treatment with a combination of sofosbuvir, peginterferon, and ribavirin had a collective rate of sustained virologic response of 90%.

The speed of development of drugs to treat HCV infection is unprecedented. The publication of clinical data with respect to sofosbuvir comes only 3 years after the publication of the chemical discovery of the compound.[5] Although the data from the four trials discussed here are encouraging, the design of the trials may have suffered from the intense competition that drug companies face in this market. In the tower of evidence-based medicine, randomized clinical trials are superior to open-label studies. However, of the four studies that are discussed here, only three were randomized, and only one was placebo-controlled. In addition, the results for sofosbuvir in these studies falls short of the findings reported for the drug in an earlier study by Gane et al.,[6] in which the rate of sustained virologic response was 100%. One of the reasons for the difference may be that the design of the study by Gane et al. was less rigorous than the designs of the studies discussed here. Also of note, the end point that was used in the four studies differed from that used in the study by Gane et al. The Food and Drug Administration only recently approved an end point of a sustained virologic response at 12 weeks (rather than the previously approved 24 weeks) as acceptable for HCV trials.[7]

Our current therapy for HCV infection revolves around side-effect management in patients receiving interferon, who require intense monitoring. Current therapies are typically offered in dedicated centers by physicians (aptly termed interferonologists) who are well versed in dealing with the toxic effects of interferon. Without alternatives to interferon therapy, we are pushing the envelope in the acceptance of risks to certain patients (e.g., those with a psychiatric history). The data from the sofosbuvir trials suggest that a radical change in clinical practice is imminent. But it may be premature to start dismantling the dedicated centers now that interferon is in retreat, since ribavirin is still part of the most successful interferon-free regimens. Data from the study by Gane et al. suggest that excluding ribavirin compromises the efficacy of sofosbuvir. The use of ribavirin has been associated with hemolytic anemia, a condition that requires close attention, especially in patients with the most pressing need for treatment, such as those with cirrhosis. Even so, the studies by Jacobson et al. and Lawitz et al. suggest an acceptable safety profile for sofosbuvir plus ribavirin, with low rates of anemia and leukopenia among patients receiving this regimen, as compared with standard-of-care therapy. On the other hand, a note of caution is appropriate, since long-term data in larger populations are lacking, and rare but irreversible adverse events still may emerge with wider use of sofosbuvir.

What are we to conclude from these studies? The low incidence of side effects, the relatively short duration of treatment, and the pangenotypic properties of the drugs are strong selling points of a sofosbuvir–ribavirin regimen and will probably lower the threshold for HCV treatment for both patients and physicians. The likely next step is to combine sofosbuvir with other direct-acting antivirals to enhance its potency. Is the interferonologist down and out? I do not think so, but it is surely time for reeducation.

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