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"There are decades where nothing happens; and there are weeks where decades happen" – Vladimir Ilyich Lenin

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Lenin could have hardly imagined that his words describing the Bolshevik revolution almost 100 years ago could be applied to the breathtaking approvals in HCV therapies in the past few weeks. Yet, if one defines 'revolution' (from the Latin *revolutio*, "a turnaround") as "a significant change that usually occurs in a short period of time", there is little doubt that we are experiencing a revolutionary epoch in hepatology, and practitioners would be wise to mark this watershed in their collective memories. After over a decade of only modest improvements upon standard interferon-based therapies, the recent FDA approvals and anticipated EMA approvals of sofosbuvir and simeprevir – albeit currently in combination with interferon and ribavirin – represent the leading edge of what will be a new era of interferon-free regimens that promise to cure more than 90% of genotype 1 patients, using regimens that are well tolerated and will rescue many patients in whom interferon is either unsafe or not tolerable. These advances have generated excitement among the lay and scientific press [1,2], patients, providers, pharmaceutical and biotech companies, and investors.

A study by Younossi *et al.* in this month's issue of the *Journal* estimates the predicted economic and clinical windfall of this revolution using Markov modeling. In this study, the authors compared the calculated incremental cost-effectiveness ratio (ICER) between patients treated with standard interferon based triple therapy (interferon, ribavirin, and either telaprevir or boceprevir) with those treated with all oral regimens for 12 weeks, based on published distributions of fibrosis stage, current costs of therapy and health care, and drug efficacies. They also distinguished between predictions based on whether patients were first screened with transient elastography (e.g., FibroScan®) as the staging method in order to limit therapy to only those with more advanced fibrosis; estimates that included the cost of liver biopsy were restricted to the sensitivity analysis. Of note, the study was performed before FibroScan® was approved in the US, and as of this writing the cost is still not determined, so the authors used the cost of ultrasound as a surrogate. The authors also made the estimate that the average total treatment cost of oral therapy was equal to the average total treatment cost of triple therapy, since the actual costs were not known at the time of their study.

The model's findings clearly favor the use of all oral regimens in all patients with HCV over the use of triple therapy, and also predict that treating all patients would be cost-effective compared to using staging-guided therapies. The all oral regimen without staging would yield an ICER of $15,709 quality-adjusted life years (QALY), well below the threshold of $50,000 often used to provide justification for new therapies. Moreover, neither a significant reduction in the cost of boceprevir/telaprevir, nor in the cost of staging would have any impact on the predicted advantage to using all oral therapy without staging guidance.

As the authors point out, the findings take on added significance with an expected increase in the detection of HCV in the United States following the endorsement of recommendations by the CDC and US Preventive Services Task Force to conduct widespread one-time HCV screening in patients between 45 and 65 years old. Modeling predictions like this study's supporting the use of a 'test and treat' strategy could greatly simplify the linkage to care following HCV diagnosis that is so vital for effective disease eradication in at-risk populations [3].

Of course, the analysis by Younossi *et al.* relies on major assumptions regarding drug efficacy, costs, and adverse events, which could well be higher in the real world than that seen in clinical trials. This was the experience in the use of triple therapy that includes boceprevir or telaprevir, where the incidence of adverse events in clinical practice after the drugs were approved was much higher, and the events more severe than what was experienced in pre-approval studies [3,4]. This unexpected problem arose in part because after the drugs were approved they were first given to those with the most urgent need for cure (i.e., cirrhotics), even though these same patients had the least capacity to tolerate adverse events.

Moreover, treatment with all oral regimens may not be so straightforward in every patient, particularly those who previously failed interferon-based regimens or with HCV genotype 1a. For example, in the article by Lok *et al.*, also in this issue of the *Journal*, the results of a phase II trial that included two experimental direct-acting antivirals (daclatasvir and asunaprevir) underscores the more labor-intensive and customized treatments

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Focus

that will be required in prior null responders, especially the need to distinguish between genotypes 1a and 1b. In the Lok *et al.* study, which was a randomized open label trial testing a series of combinations with or without interferon, 99% of the patients had the non-CC IL-28 genotype associated with interferon resistance, which explains their prior non-responses. In these difficult-to-treat patients, those with genotype 1a required interferon-based combinations to achieve an SVR. Thus, prior non-response was a tipoff to the need for more detailed diagnosis (e.g., viral and possible IL-28 genotyping) and customized therapy, yet as we screen and uncover more untreated HCV, some will also have genotype 1a and a non-CC IL-28 genotype and will possibly fail an all oral combination. Indeed, the simeprevir drug label will indicate that in genotype 1a patients resistance testing should be performed for the 'Q80K' mutation. If present, then "other therapies should be considered." Thus, should our initial algorithm include both HCV and IL-28 genotyping, or should we wait until such patients fail initial therapy and then consider retreatment with an interferon-based regimen? If so, will viral resistance from initial therapy limit efforts to retreat? These are the kinds of nuanced questions, which color the interpretation of the Markov modeling used by Younossi, although they do not undermine it.

As we enter this momentous transition towards an 'interferon-free' world, it is also worth looking back to ask which advances were absolutely critical to bringing us to this juncture. I would contend that three seminal discoveries were essential: (1) The discovery of the HCV agent by Houghton, Choo, Kuo, Bradley and colleagues [5], a Nobel-worthy achievement both because of its public health impact and for the brilliant new methodology they formulated to clone the virus; (2) The development of cell based culture systems that supported HCV, first using the replicon [6] and then later the infectious JFH1 virus systems [7,8], which enabled high throughput drug screening and the discovery of obligate cellular receptors for HCV [9]; (3) The characterization of HCV protein structures, which greatly facilitated the design of direct-acting antiviral drugs.

Does this mean that all the other investments in HCV research were irrelevant? Not at all. The discovery of HCV could not have happened without years of clinical characterization of non-A non-B hepatitis cases and studies in non-human primates, among others. Similarly, revealing how HCV evades immune clearance and how it drives intracellular innate immune signaling have already borne fruit in helping us understand the pathogenesis of other viral infections, and will also be vital in developing a prophylactic HCV vaccine.

Another important implication of these three seminal discoveries is that they reflect a healthy synergy between the academic and commercial research spaces. Both the discovery of the virus and the development of new drugs took place in the biotech/pharmaceutical sphere, yet they could not have happened without equally important discoveries in academia, including the clinical studies before and after the discovery of the virus, and the characterization of cell culture systems to enable drug screening. In fact, one could argue that the HCV success story represents an ideal consequence of a healthy, interdependent ecosystem between academic and commercial research.

This brings us back to the words of Lenin and the exciting times we live in as investigators or clinicians devoted to liver disease. We can only hope that decades do not pass again before witnessing another revolution in our specialty, but just in case let's enjoy this rare view while we can.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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