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Introductory Chapter: Treatment of Viral Hepatitis - Current Challenges and Future Perspectives

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1. Hepatitis C therapy

Cure of hepatitis C has come true!

Clinical care for patients with hepatitis C (HCV) has advanced remarkably during the last two decades, as a result of better understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention. With the introduction of genotype 1 effective directly acting antiviral agents (DAAs) in 2011, the management of HCV infection started to change. By 2013, second-generation pangenotypic DAAs became available, and the biggest problem was solved: interferon (IFN) became no longer necessary.

Unlike IFN regimens, which rely on upregulating the patients' own immune system, these DAAs block different stages of viral replication. There are four major groups of DAAs namely: NS5B nucleotide inhibitors, NS5B nonnucleoside inhibitors, NS5A replication complex inhibitors, and NS3/4A protease inhibitors [1]. Specific treatment regimens vary, depending on factors such as HCV genotype, and may include multiple drugs [2]. Multiple regimens have been approved and several new regimens with high potencies, less resistance, and better safety profile are in the process of approval. Prof. Kamal elegantly describes them in detail in Chapter 2.

Sustained virological response (SVR) rates achieved in phase III clinical trials generally exceeded 90% (although real-world rates may be lower) along with reduction in treatment duration to 12 weeks or less and with fewer adverse events. An SVR is generally associated with normalization of liver enzymes and amelioration or disappearance of liver necroinflammation and fibrosis in noncirrhotic patients [3]. The use of DAAs in patients with cirrhosis, as discussed in Chapter 4, has also shown excellent results with good safety profile. SVR also improves HCV-induced portal hypertension [4]. DAAs have also begun to change the landscape of management of the HCV transplant candidate on the waiting list. Prof. Al-Hamoudi provides an update on this in Chapter 5. Even patients with HCV infection and advanced kidney disease now have alternative treatment options.

Thus, the era of HCV eradication and cure has begun. And in 2017, hepatologists can treat *all* patients irrespective of fibrosis score—but the job is not over yet. Real-world experience has revealed several challenges and unmet needs!

1.1. Challenges:

(a) Limited or absent access to therapy in the majority of infected patients

Unfortunately, the very high cost of the new DAA drugs is creating a barrier for introduction of treatment in most limited resource settings and may prove an obstacle on the path for elimination of HCV infection worldwide. Of course, successful treatment should prevent many late HCV complications, but even if treatment actually proves cost saving in the long run, it is too expensive and infeasible to treat all patients immediately [5].

Hence hepatitis C treatment prioritization, as the European Association for the Study of the Liver states, is necessary when resources are limited [6]. However, new data suggest that this approach may be suboptimal, if not carefully executed. Treatment prioritization is complex and may not be fair. Treating first those with the most need makes sense. But, those who need it most may also be those who benefit the least because of issues as extensive liver damage, comorbid illness, older age, or have already developed hepatocellular carcinoma? Targeting populations with high HCV prevalence like drug users, prisoners, and migrants also makes sense since they are most likely to spread infection to others. But, those most likely to transmit to others often have low disease stage. Besides they are most likely to abrogate the personal benefits of treatment by being reinfected. Treating those who have the most symptoms also makes sense, but unfortunately symptoms do not always improve with cure. And there is another major issue: who should decide whom to prioritize? [7]. Health care providers often impose socioeconomic and racial biases when prioritizing treatments [8]. Moreover, health care providers prefer not to be the barrier between patients and life-saving therapies.

While *not* all patients require immediate treatment, an ideal strategy should treat patients before they progress toward end-stage liver disease when even highly effective treatments can confer only marginal benefit. In response, many countries have instituted coverage policies that authorize treatment only for the advanced patients, putting off therapy for less severely ill patients [5].

Aggressive action is warranted to see progress toward HCV elimination. Only if we use *efficacious therapy* in a *significant* proportion of patients will we *significantly* decrease the burden of the disease. So efforts should be made to make DAAs cost effective in all clinical scenarios and accessible to all patients. In places like Egypt and India, generic versions of the DAAs sofosbuvir and daclatasvir are being mass produced for <1% of the current US retail price and are available for a higher proportion of patients.

Another solution to reduce treatment cost is by shortening the duration of treatment without affecting efficacy. A study in China demonstrated 100% SVR with triple DAAs for only 3 weeks if the patient without cirrhosis achieved ultra-rapid virological response (HCV-RNA < 500 IU 48 hours after starting treatment) [9]. By shortening the duration of therapy from the currently

recommended 12 to 3 weeks, the cost of therapy could be markedly reduced as well as the rate of adverse events. Large clinical trials should further study the application of this response-guided treatment approach in patients with different ethnic backgrounds and with different genotypes.

(b) Emergence of drug resistance and DAA failure

Despite improved SVR rates with DAA-based combination regimens, treatment fails to eradicate HCV infection in 5–15%, depending on the treatment regimen and treated population. Treatment failure is generally associated with the selection of HCV resistant-associated substitution (RAS) (or resistant-associated variant (RAV)), that is, viral molecular substitutions or variants that have reduced susceptibility to the DAA(s) administered. NS5A inhibitors have a low barrier to resistance, and the variants they select confer cross-resistance across all members of the drug class. Thus, NS5A resistance currently appears as the principal challenge of IFN-free, DAA-based therapy and they tend to persist for several years after treatment failure. In contrast, RASs selected by NS3/4A protease inhibitors persist for a much shorter time and are progressively replaced by wild-type virus within a few months posttherapy. Additionally, RASs selected by the NS5B polymerase inhibitor sofosbuvir have poor viral fitness; thus, they rarely emerge in the presence of the drug and tend to rapidly disappear if selected [10]. The utility of HCV resistance testing, i.e., the determination of the sequence of the DAA target region prior to retreatment in patients who failed on any of the DAA-containing regimens is unknown. Chapter 6 summarizes the retreatment in case of drug failures.

(c) HCV eradication and the risk of hepatocellular carcinoma (HCC): issues with direct acting antiviral (DAA) therapy?

Several recent publications raise concerns about unexpected high rate of HCC recurrence after undergoing direct-acting antiviral therapy. Reig et al. showed early tumor “recurrence” in patients with HCV-related hepatocellular carcinoma (HCC) [11]. Conti et al. showed that in patients with HCV-related cirrhosis, DAA-induced resolution of HCV infection does *not* reduce recurrence of HCC, and patients previously treated for HCC have still a high risk of tumor recurrence, in the short term [12]. Kozbial et al. showed an unexpected high “occurrence” in patients with advanced liver diseases after SVR [13].

In contrast, Cheung et al. found that DAA therapy in patients with decompensated cirrhosis led to sustained improvement in liver function, with no evidence of increase in HCC development in Chinese patients [14]. Also, the French ANRS study analyzed more than 6000 DAA-treated patients who underwent curative therapies for HCC and they found no increased risk of HCC [15].

Altogether these studies convey a strong message that great attention is needed to address the issue of HCC recurrence/occurrence. There is an urgent need for large prospective studies evaluating the impact of DAA therapy on the risk of HCC in patients with HCV-related cirrhosis. For the time being, the risk of HCC development justifies HCC screening after viral clearance in patients with HCV-related cirrhosis.

(d) There is no vaccine yet. Is a prophylactic vaccine still necessary?

Obviously, therapy is not enough to surmount the burden of HCV. Is it technically possible to have vaccine? If HCV vaccines are available in the future, then vaccination program in high-risk populations would probably have a great impact on preventing and eradicating HCV infection. An experimental protective vaccine, as shown in Chapter 14, demonstrated promise in preliminary human safety trials, and a phase II clinical trial is under way to further determine the efficacy of the vaccine.

1.2. Future perspectives:

Therefore, although the DAAs have opened up new horizons for HCV cure, challenges persist in the real-world setting. It is becoming clear that developing therapeutic strategies with different modes of action would be necessary to address the various limitations of current DAAs. Third generation pangenotypic antivirals are currently in final phases of development: voxilaprevir [16], glecaprevir [17] (both NS3/NS4 protease inhibitors) and pibrentasvir (NS5A inhibitor) [17]. Antivirals with alternate mechanism of action, such as by restricting viral entry or cell-to-cell spread could help expand the scope of antiviral strategies for the management of hepatitis C. Chapters 14 and 15 describe some of the new paradigms in antiviral strategies to preclude HCV entry, such as through monoclonal antibodies and small molecules.

With these strategies, it is foreseeable, in a not too distant future, that they will help provide a better management of hepatitis C.

2. Hepatitis B therapy

An overview of the six currently approved treatments is presented in Chapter 7. The advent of anti-HBV treatment drugs has made *significant progress* in improving the health and life expectancy of patients with HBV.

But there is no cure for Hepatitis B till now!

Chronic hepatitis B remains a difficult to treat disease because at this time no treatment provides both an optimal virological and immunological control. There is a high rate of relapse following any antiviral therapy. In addition, there are no approved therapy stopping rules, especially in HBeAg negative patients treated with nucleoside and nucleotide analogs. An early stopping rule using the combination of serum HBsAg and HBV DNA was proposed and is discussed in Chapter 9.

While there have been significant advances in the management of hepatitis B with available nucleos(t)ide analogues, there remains much work to be done to prevent HCC. Viral suppression alone has proven not effective for the absolute prevention of HCC.

Additionally, the required long-term therapy imposes not only financial burden but also may put patients at risk for potential drug resistance and unknown toxicity. Therefore, more effective treatment regimens aiming for HBV cure are urgently needed. New investigational therapies are in the pipeline as discussed in Chapter 17. With multiple new therapies in the pipeline,

the future of treating hepatitis B is an exciting one, and there is hope that it will become a disease of the past but this will not be too soon! The new therapy will not be available soon.

Another challenge is a demand for screening pregnant females and newborns for HBV. Pregnancy screening for HBV is very defective in most countries; it is not practiced except on individual basis. Chapter 10 reviews current management strategies for hepatitis B in the pregnancy and the postpartum.

Conclusion

So, in conclusion, the highly effective and well-tolerated direct-acting antiviral drugs (DAAs) for the treatment of the hepatitis C virus have revolutionized therapy for HCV. Several novel therapeutic strategies for each of HBV and HCV are under development. But until the developing antiviral strategies are available, there is much more that can be done.

The public health burden posed by viral hepatitis should be recognized as a priority. The leading professional organizations in liver disease, the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL) urge governments, health care organizations, and nongovernmental organizations to adopt recommendations for immunization, screening, diagnosis and treatment and to make them available and affordable for public health programs [18].

Overall, the achievements and improvements in the field of HCV and HBV care predict that the future of HCV and HBV therapeutics is becoming brighter every day.

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