Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX

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Other Therapeutic Pipelines

Because interferon-α has been an essential component of HCV treatment regimens for many years, research has focused on developing alternative or improved forms of interferon. The pegylated form of interferon-α (either α2a or α2b) with improved efficacy, has replaced regular interferon-α in practice. Other forms of interferons, such as consensus interferon, albuferon, and control-release interferon-α have been or are being tested in the clinics.[1] None of them have made it to the mainstream for various reasons. Recently, a different form of interferon, interferon-λ, has been developed because of the strong association of genetic variations in one of the IFN-λ genes (λ3 or IL28B) with interferon-based treatment response.[2] In addition, IFN-λ may have a better side-effect profile because of the more restricted expression of its receptors throughout the body.[2] Early clinical studies suggest that it may indeed have fewer side effects but similar efficacy as compared to peginterferon-α.[3] Interferon inducers, such as agonists of toll-like receptors (TLR3, 7, 8, and 9), are currently being evaluated in clinical trials, but their advantage over interferon remains to be demonstrated.[4] The major question is whether interferon will still be necessary in the future should, as is expected, interferon-free regimens achieve an efficacy rate of 90-100% in all HCV-treated patients.

Other therapeutic strategies targeting the host are being explored. Therapeutic vaccines, aiming to boost the host anti-HCV immune responses, are in early clinical trials, and in general, appear not very potent.[5] As discussed earlier, host targets that are important in HCV propagation may expand the therapeutic armamentarium and

improve response. The advantage of host-targeting antivirals is a relative lack of drug resistance. On the other hand, it may be associated with more toxicity. Since HCV propagation is closely linked to lipid metabolism, lipid-altering agents, like statins and PPAR-γ agonists, have been studied in clinical trials but have shown minimal benefits.[6,7] Novel host targets identified by recent functional genomic approaches may provide promising alternatives to HCV therapeutic development.[8] For example, PI4KCA, a membrane-associated signaling molecule, was identified as a crucial host factor in HCV replication and pharmacologic inhibition of its activity potently blocks HCV replication.[9]

Table: Ishak Scoring System for Fibrosis Stage[10]

Stage	Description
0	No fibrosis
1	Fibrous expansion of some portal areas with or without short fibrous septa
2	Fibrous expansion of most portal areas with or without short fibrous septa
3	Fibrous expansion of most portal areas with occasional portal to portal bridging
4	Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)
5	Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis)
6	Cirrhosis

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