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Silibinin mode of action(s) against HCV: A controversy yet to be resolved

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Dear Editor

Wagoner et al.[1, 2] suggested that Legalon-SIL (SIL), a commercially available intravenous preparation of silibinin, has an effect on HCV entry and cell-to-cell spread *in vitro* with only marginally suppression of HCV NS5B RNA-dependent RNA polymerase (RdRp) activity, a finding that is in contrast with Ahmed-Belkacem et al.[3] findings. Three clinical studies have reported the viral response during SIL therapy[4-6]. The protocols were similar and consisted of daily injection of SIL for 7 days followed by Peg-IFN+ribavirin; however in[5] ribavirin was administered before and during silibinin treatment. Viral decline after the initiation of SIL was monophasic until day 7 in the two case reports and in the majority of subjects in [4] (Fig. 1, red squares). Interestingly, a monophasic pattern of viral decline (Fig. 1, blue curves) was also observed in about half of patients (N=31) given 14 days of monotherapy with RG7128, a nucleoside HCV-RdRp inhibitor (manuscript in preparation), and in 3 subjects (N=5) in Le Pogam et al. (Fig. 1A in[7]). This monophasic decline is strikingly different from the biphasic viral decline typically observed in patients treated with protease inhibitors or (pegylated)interferon-α-based therapies[8] (Fig 1, triangles). The fact that both SIL and RG7128 led to a monophasic HCV decline in some patients is interesting and tends to support Ahmed-Belkacem et al[3] findings.

According to the standard HCV infection model[9], a monophasic viral decline pattern results when viral infection is blocked, which tends to support the Wagoner et al.[1, 2] findings. On the other hand, one can also predict a monophasic decline of virus if one assumes in the standard viral kinetic model a gradual reduction in viral production (unpublished observation), rather than an immediate high antiviral effectiveness in reducing viral production as it is the case with interferon-α or protease inhibitors. This gradual reduction in viral production could be related to drug pharmacokinetic and pharmacodynamic (PK/PD) properties. Such PK/PD properties leading to a progressive reduction in viral production could explain the similarity in the pattern of viral decline observed under treatment with SIL and RG7128 and possibly will shed light on why some patients treated with either of these two agents had a monophasic viral decline pattern.

In summary, to further investigate this controversy we suggest that PK/PD studies of SIL are needed to better understand the nature of the observed monophasic viral decline in treated patients. If SIL resistant strains can be identified, the nature of the resistance mutations would provide information about the MOA. If resistance mutations are found in the HCV polymerase it would favors an HCV-RdRp inhibitor mechanism, whereas if resistance mutations are in HCV E1/E2 it would support an entry inhibitor mechanism. Further *in vitro* experiments[10] that include detailed kinetics of both intracellular and extracellular HCV

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RNA during treatment with SIL are likely to provide more insights into its MOAs against HCV.

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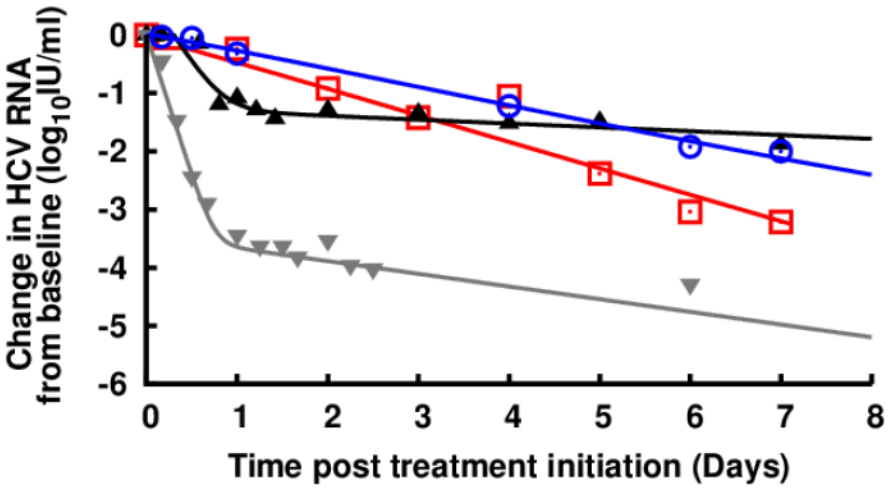

Figure 1.

Representative serum HCV RNA decline from baseline during the first week of treatment with silibinin monotherapy[6] (red squares), RG7128 1500-mg BID (blue circles; manuscript in preparation), daily 10MIU IFN[9] (black triangles) and telaprevir+PegIFN[8] (gray triangles). Solid lines were used to emphasize plausible phases of viral decline.