Reply to: “Neuroinflammation in HCV-infection – Peril or protection?”

Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition

To the Editor:

We are grateful for the opportunity to address the findings of two recent studies on neuroinflammation and cognition in HCV referred to in the letter above, and published subsequent to the submission of our paper to this Journal.

The first study of Weissenborn et al. examined differences in cerebral metabolites and cognition in 53 HCV positive subjects compared to 26 healthy controls [1]. Consistent with numerous other studies on this topic in the literature, HCV positive patients were more fatigued, more depressed and performed significantly worse in tests of attention, reaction time and working memory than HCV negative controls. Moreover, higher levels of choline (Cho) were shown in basal ganglia and white matter of HCV positive patients than in controls, indicative of a neuroinflammatory effect of HCV.

Subsequent to our publication of improved cognition in addition to a reduction in cerebral metabolites following treatment-induced viral clearance, Dr. Weissenborn re-analyzed her data. The reader may recall that we reported significant improvements in the domains of verbal learning and memory in sustained virological responders (SVRs) but not in NR/Rs (non-responders/relapsers). Moreover, we found significant reductions in choline/creatinine (Cho/Cr) and myoinositol/creatinine (MI/Cr) as measured from the basal ganglia of SVRs, which was not observed in NR/Rs [2]. Weissenborn’s re-analysis included an additional nine HCV PCR negative subjects, six SVRs, and 18 non-responders (NRs) who were not part of the published study group, but who had undergone the same study protocol. In this retrospective analysis, SVRs performed better than NRs on psychometric testing (especially on testing of verbal recall) but these differences were not significant. In the MRS component of their study, PCR positive subjects demonstrated significantly higher levels of Cho, MI and Cr than PCR negative patients but these differences were noted in the occipital cortex rather than the basal ganglia, as in our study.

Several problems arise when comparisons are drawn between two very different studies. Firstly, Dr. Weissenborn’s data comes from a cross sectional study, comparing group means of subjects that were matched for age only. Data analysis obtained from a single point in time cannot be reliably compared to our longitudinal study, where each subject was tested at multiple time points and served as their own control. Secondly, as outlined by Dr. Weissenborn, technical differences in voxel positioning and data acquisition (metabolite quantification) may account for varying results. The voxel placed in the basal ganglia in our study did indeed contain a section of internal capsule between the caudate and putamen, as have earlier studies of HCV patients [3]. The placement of this voxel was carefully reproduced for each study in the same patient. The presence of white matter in part of the voxel should not introduce a systematic difference in metabolite ratios over time and does not invalidate our findings of a treatment effect on MRS ratios. In addition, we expressed each of the metabolites of interest as a ratio of the internal control creatine, as have most investigators in this field. While it may be more advantageous to perform absolute quantification of metabolite concentrations, two recent studies have shown that ratios to creatine provide similar findings to absolute quantification, even in studies of cerebral inflammation [4,5].

It would be more accurate to compare our results to the recent findings of Pattullo et al., whose longitudinal design had much in common with our study protocol [6]. They reported minimal changes in cognition and markers of cerebral inflammation in 31 SVRs when compared to nine NRs. Possible explanations for differences between Pattullo’s study and ours are as follows. Firstly, their psychometric testing occurred at two time points 12–18 months apart, as opposed to ours which had three testing points over a shorter time frame (9–15 months). It is possible that our results are partially reflective of practice effects and not resolution of cognitive abnormalities. If this is the case, it is still worth noting that SVRs were more likely to benefit from the effect of practice than NR/Rs. Secondly, due to stringent exclusion criteria, HCV positive subjects in Pattullo’s study had very healthy neurocognitive scores at baseline and it is therefore not surprising that further improvements in cognition were not observed in spite of viral clearance. This is in stark contrast to our findings, whereby, in spite of excluding co-morbidities known to affect cognition, 50–71% of the HCV study group had impaired scores on verbal learning domains at baseline when compared against normative means. Furthermore, while Pattullo and colleagues did not find any significant differences in metabolite ratios measured from the basal ganglia (globus pallidus) in SVRs when compared to NRs in this very comprehensive study, they did however observe an increase in basal ganglia N-acetyl aspartate (NAA) in SVRs over time, a finding that is in keeping with the concept of improved neuronal integrity following viral clearance.

In conclusion, we accept that our study numbers are small. We have presented results of a pilot study that merit further exploration in larger studies with a longer follow-up to assess for “delayed” benefits of HCV eradication, or studies employing the techniques of functional MRI allowing direct observation of brain function, before and after anti-viral therapy.

Conflict of interest

Dr. Afdhal and Dr. Byrnes have received grant support from Schering Plough. Dr. Afdhal has been on the Advisory Board and a Consultant for Schering Plough and now Merck.

References


Letters to the Editor


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Why 88% of US military veterans with HCV are not treated

To the Editor:
The article in the February issue of the Journal of Hepatology reported that less than 12% of American military veterans identified with HCV were treated with antiviral therapy [1]. The Veterans Administration does not want to spend adequate funds to cure patients with hepatitis C. Dr. Kenneth Kizer, Under Secretary for Health in the US Department of Veterans Affairs (VA), gave HCV a high priority but unfortunately he left the VA in 1999. Subsequent leadership has not shown enthusiasm for treating HCV.
The Director of Pharmacy and the Chief of Staff at my local VA hospital told me that I spent too much money treating HCV. Boceprevir and telaprevir are both on the hospital formulary but telaprevir prescriptions are routinely denied because it is more expensive. Patients must jump multiple hurdles before qualifying for antiviral therapy. No one would refuse to give coronary artery stents or bypass grafts to a veteran who smokes but veterans who do not completely abstain from alcohol for three months are refused antiviral therapy. In spite of difficulties, 585 of 1372 (43%) HCV RNA positive patients received antiviral therapy between 1998 and 2010 at our local VA hospital; 226 of 583 treated (39%) achieved SVR [2]. 36% of deaths were from HCC or liver failure. Veterans with sustained viral response had substantially improved survival. Effective antiviral therapy improves prognosis [3,4]. Less than 2% of Americans die from liver disease, but more than one third of veterans with HCV die prematurely from complications of cirrhosis [2,5]. According to a 2010 national VA report, deaths in veterans with HCV have more than tripled, “Between 2000 and 2008, the annual number of all cause deaths recorded for Veterans with chronic HCV rose from 1259 [1129 per 100,000 in VHA care] to 5967 [4049 per 100,000 in VHA care], respectively” [6]. Legislation should be passed allowing veterans with HCV to prequalify for their choice of Medicaid or Medicare so that they can obtain antiviral therapy in the private sector. Since Dr. Kizer is no longer in charge of the VA, it is very clear that the VA is not going to treat very many of them.

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Speakers Bureau Vertex Pharmaceuticals.

References

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