the CNS by natalizumab [peak α4-integrin saturation on lymphocytes is achieved 3 days after initial IV infusion and maintained at >80% for 4 weeks, sufficient to prevent significant CNS transmigration of lymphocytes[5,6]]; (2) ongoing steroid treatment of CNS inflammation; (3) effective endogenous remyelination mechanisms in this patient (suggested by complete and timely recovery from previous disabling relapses); and (4) early resolution of encephalopathy enabling effective therapy and accelerated recovery.

The decision to suspend or continue natalizumab in pregnancy must consider risks to both fetus and mother. Although the risks to the fetus of natalizumab exposure appear low and reversible,[7] further evidence is required, particularly long-term data on children exposed in utero. Careful counselling at the time of natalizumab initiation in women of childbearing age is imperative.

From ABMU (T.H.M., R.S., S.S., O.R.P.), Morriston Hospital, Swansea; Cardiff University (T.H.M.); and Hywel Dda University Health Board (C.O.), Withybush Hospital, Haverfordwest, UK.

Author contributions: Thomas Massey: study concept and design, data accumulation and interpretation, drafting/revision of manuscript. Rachel Smith: data accumulation and interpretation, revision of manuscript. Shaheena Sadiq: data accumulation and interpretation, revision of manuscript. Christopher Overton: data accumulation and interpretation, revision of manuscript. Owen Pearson: study concept and design, data accumulation and interpretation, drafting/revision of manuscript.

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Correspondence to Dr. Pearson: Owen.Pearson@wales.nhs.uk

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Felix Kleefeld
Sophie Heller
Heiko Jessen, MD
Patrick Ingiliz, MD
Antje Kraft, PhD
Katrin Hahn, MD

EFFECT OF INTERFERON-FREE THERAPY ON COGNITION IN HCV AND HCV/HIV INFECTION: A PILOT STUDY

OPEN

Approval of direct-acting antivirals against the hepatitis C virus (HCV) has dramatically changed the management of HCV infection due to high cure rates and a favorable safety profile. Their influence on neurologic aspects is notably relevant, as studies demonstrated active HCV replication within the CNS[1] and alterations in cerebral metabolism consistent with neuroinflammatory conditions.[2] These findings may be causative for cognitive deficits in HCV-infected patients.[3] Similar impairment has been demonstrated in patients coinfected with HIV, with a prevalence as high as 60%.[4] Therefore, these patients may particularly benefit from HCV eradication. To date, studies addressing the issue of reversibility of cognitive deficits after HCV therapy are based on interferon treatment, which itself can cause continuing cognitive impairment.[5] The important question whether these deficits are indeed reversible after HCV eradication remains unsolved to date.

Methods. We conducted an open observational trial with HCV and HCV/HIV coinfected patients and planned HCV treatment. Patients with liver cirrhosis (defined as fibroscan >12.5 kPa), a history of substance dependence, or cerebral diseases were excluded. HIV-infected patients had to have undetectable plasma HIV levels for at least 6 months. We assessed a comparison group of healthy controls (n = 30) for baseline, but not for follow-up. The neuropsychological test battery

Table Cognitive performance at baseline before therapy

Domains evaluated[a]	Infected (n = 25)	Control (n = 30)	*p* Value
Visual learning/memory			
Rey-Osterrieth Complex Figure: immediate recall	51.73 (11.48)	62.68 (11.00)	0.001
Rey-Osterrieth Complex Figure: delayed recall	50.50 (10.82)	62.00 (10.81)	0.000
Attention/working memory			
Digit span: forwards	50.71 (12.04)	59.88 (7.84)	0.002
Digit span: backwards	49.63 (11.00)	61.13 (8.66)	0.000
d2 Test of attention: concentration	43.24 (8.33)	51.50 (8.60)	0.001
Executive function			
Color-Word Interference Test	47.60 (11.00)	54.83 (9.69)	0.012
Trail-Making Test Part B	49.22 (12.69)	57.33 (7.63)	0.005
Processing speed			
Trail-Making Test Part A	48.35 (10.50)	55.20 (8.04)	0.008

Values are presented as mean (SD) of *t* scores for all tests.
[a] Not significant: language/verbal fluency, logical thinking/nonverbal intelligence level.

included standardized tests and—to minimize practice effects—alternate versions for follow-up testing, covering 7 domains (table). We used age-corrected norms. To test for baseline and longitudinal differences, we used *t* tests for dependent and independent samples, respectively. Participants completed self-report assessments of cognitive symptoms, instrumental activities of daily living, fatigue, depression, and quality of life. Testing sessions took place at baseline and at the earliest 12 weeks after the end of HCV treatment.

Results. We have seen 25 HCV-positive outpatients between 2015 and 2016 before treatment. Fifteen were coinfected with HIV. All but one participant were male. Groups did not differ significantly in age or years of education (patients [mean age 43.8 years (SD 11.7); mean education 15.1 years (SD 2.1)]; controls [mean age 39.5 years (SD 9.9); mean education 16.1 years (SD 2.0)]). Mean nadir CD4 of the coinfected group was 328 cells/μL (SD 215); baseline CD4 cell count was 846 cells/μL (SD 242) and remained stable over time. At baseline, the patient group showed significantly poorer performance in the domains of visual and working memory, processing speed, attention, and executive functioning (table). We did not observe a difference between monoinfected and coinfected patients.

To date, 12 participants have completed therapy and undergone follow-up. Treatment regimens were well-tolerated and included the following: ombitasvir/paritaprevir/ritonavir + ribavirin (n = 2), ledipasvir/sofosbuvir (n = 9), or sofosbuvir + ribavirin (n = 1). Mean therapy duration was 10 weeks (8–12 weeks); all patients were HCV-RNA-negative at week 12 after treatment completion.

At follow-up assessment, patients did not show cognitive decline in any domains compared to baseline; neither did any patient report subjective impairment during or after the therapy. On the contrary, 2-tailed *t* tests indicate a significant ($p < 0.05$) improvement in the domains visual memory, processing speed, attention, and executive functioning. In addition, we observed a significant ($p = 0.022$) decline in self-reported fatigue severity. There was no significant change in the level of depression, but an increase in self-reported quality of life.

Discussion. In this study, we investigate the effect of an interferon-free treatment on cognitive function in HCV-monoinfected and HCV/HIV coinfected patients. Our data show that HCV-infected patients without comorbidities had significantly poorer cognitive performance than controls. Against our expectations, HIV coinfection did not increase the extent of cognitive deficits. These findings partially contradict conclusions made by other studies. A recent study[6] showed that HCV coinfection did not have an effect on cognitive function in a cohort of HIV-infected patients, which led the authors to question an influence of HCV on cognition per se.

In contrast, our data suggest a significant influence of HCV infection on cognitive function, which seems to outweigh that caused by HIV infection. Our first follow-up data support this assumption, showing an improvement in those cognitive domains that were impaired before HCV eradication. Our study was explicitly designed to detect differences attributable to HCV eradication. In contrast to the cross-sectional approach of most previous studies, we therefore chose a longitudinal approach.

Nevertheless, these first data have to be interpreted carefully due to small sample size. Practice effects might partially contribute to the observed improvements. However, reported effect sizes are relatively small (Cohen $d = 0.00–0.24$)[7] compared to the ones seen in our cohort ($d = 0.20–1.79$). To verify an improvement, more follow-up data need to be considered using a reliable change index approach[8] to differentiate between practice effects and treatment-related cognitive changes.

From Universitätsmedizin Charité (F.K., S.H., A.K., K.H.); Praxis Jessen2+Kollegen Berlin (H.J.); and Medizinisches Infektiologiezentrum Berlin (P.I.), Germany.

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Correspondence to Dr. Hahn: Katrin.hahn@charite.de

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