

MR Imaging of Drug-Induced Suicidal Ideation

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Abstract

Two patients with a history of suicidal ideation (SI) underwent functional MR imaging while undergoing treatment with interferon alpha 2 (IFN) for Hepatitis C virus infection (HCV). Patient #77 had a remote history of SI, but no current SI when treated with IFN. Patient #288 experienced an IFN-heightened SI, although she denied intent, a plan or a means. Visual stimuli were presented during functional MR imaging (fMRI) that were designed to invoke thoughts of suicide and violence. Patient #77 showed activation expected for visual stimulation alone, whereas patient #288 showed heightened activation for some of the visual stimuli with violent emotional content. Functional MR imaging shows promise to screen for a number of medication-induced CNS adverse effects (AE).

INTRODUCTION

Treatment of infections such as HCV with currently available medications can be associated with serious medical/clinical consequences, including psychological sequelae (prescribing information - PI). The use of interferon has been associated with SI (PI; Janssen et al., 1994; Fukunishi et al., 1998; Schafer et al., 2000; Ademmer et al, 2001; Bagheri et al., 2004; Dieperink et al., 2004; Laguno et al., 2004), although the incidence is not well-characterized (Helbling et al., 2002). The rate at which drug-induced SI progresses to a suicidal act is also not known. Other than avoiding use of IFN in individuals with significant underlying depression (Barraclough et al., 1974) or other risk factors for suicidal thought (CDC 2007), there is currently no reliable way to prevent an individual from responding to IFN by developing SI. It will therefore be of immense value to be able to predict and monitor in a quantifiable manner a clinically significant suicidal response to IFN in patients prior to the initiation of treatment, and also during the drug development cycle.

Functional neuroimaging has been successfully applied to the study of mood-disorders, including endogenous [Fu et al et al., 2004] and medication-induced (Marks et al., 2007a) depression, anxiety, and drug-seeking behavior. The application of fMRI for SI follows logically (Mann 2005). We have previously demonstrated (Marks et al., 2007a) interesting differences between MR imaging of major depressive disorder (MDD) and that of medication-induced depression and anxiety, implying that the underlying

causative mechanisms and treatment may differ. This report describes an initial effort to adapt fMRI to identify and monitor the course of SI induced by medications. This approach holds the potential of introducing new paradigms for understanding and treating SI.

METHODS

Three hundred ninety patients with HCV were evaluated for treatment at the Hepatitis Clinic of Cooper Green Mercy Hospital (CGMH), an inner city safety net medical facility in Birmingham, Alabama. Patients did not automatically receive antidepressants as a prophylactic action prior to therapy with IFN and weight-based ribavirin (RBV). Treatment for HCV used standard protocols (NIH Consensus Statement).

Before antiviral treatment was offered, all patients were provided with a discussion, brochures and videos of HCV infection, treatment options, an understanding of the potential adverse effects of medicine including suicidal ideation, alternatives to treatment, and were required to attend a class for the lay person covering all aspects of HCV disease and treatment. We entered into our database the patient demographics, viral load at start, during and after treatment, decision to treat, risk factors for suicide, urine drug screens, adverse effects and other data for all patients with viral hepatitis seen in the hepatitis clinic at CGMH for the four year period 2004-2007. A directed search of the data for DSB was prepared for this publication; no change in therapeutic decision was based upon the collection of this

data, and due to the low numbers a statistical data analysis was not performed. The hospital Institutional Review Board (IRB) approved the use of anonymous demographic and incidence data collection for the purpose of preparing this publication.

Two patients (#77 and 288) with Hepatitis C Infection, candidates for therapy with IFN- α 2, received IFN and other treatment as part of their usual care. Patients were seen routinely at 2, 4, 6, 8 weeks of treatment with IFN, and monthly thereafter, unless their medical condition required more frequent visits. At each visit, patients were interviewed, questioned about anxiety, depression, insomnia, agitation, suicidal thoughts, drug craving and other psychiatric symptoms reported to be associated with use of IFN, and a subjective assessment of the onset of mood disorders was made.

For fMRI, potential test subjects were explained the study purpose and design, risks and benefits, and asked to give written informed consent for participation in the IRB-approved protocol: "Use of fMRI to Predict Neurologic Adverse Effects of Interferon Used to Treat Patients with Hepatitis C and HIV-infected Patients Treated with Sustiva". The specifics of the two patients chosen for participation was discussed in detail with the IRB before they were entered into the protocol. Patients were assessed for risk factors, in addition to the regular aspects of an initial office visit for intake for evaluation of hepatitis C.

To perform fMRI, each test subject lay within a GE Cigna 3-T Signa 11X Excite MRI scanner, wearing a phased array whole head coil, mounted with a 45 degree mirror. This arrangement allowed test subjects to see images displayed onto a rear projection screen positioned by their feet. fMRI was performed while viewing of the test stimuli in order to capture functional data, as described by Marks et al (2007a). A short localizer MRI scan was performed to verify that the field of view was within the skull, and to assure the absence of "ghost" images. A high-resolution full volume structural MRI scan was then obtained for each subject, using fast SPGR imaging (146, 1.0-mm thick axial slices, no spaces, TR = 8, TE = 3.2, FOV = 24 cm, 256 x 256 matrix). These T1-weighted images provided detailed anatomical information for registration and 3-D normalization to a standard atlas.

Patients were then shown photos images (most were selected from the International Affective Picture System) with content designed to recall thoughts of suicide, homicide or

depression. Pictures were generated by PC using PowerPoint (Microsoft) and projected onto a rear projection screen placed at the foot of the test subject, as described in Marks et al (2007a). Pictures were viewed by means of a mirror system mounted on the head coil.

Sequence of visual stimuli presented to patients #77 and 288

Figure 1

Patient 77	Patient 288
	suicide 2
	suicide 3,4
homicide 1,2	homicide 1,2
homicide 3,4	homicide 3,4
Depression 1, 2	Depression 1, 2
suicide 3,4	

Changes in the blood oxygen level dependent (BOLD) MRI signal were measured using a gradient-echo echoplanar sequence. Continuous fMRI scans lasted 110 seconds each. EPI parameters were: TE 35, TR 2000, multiphase screen, 55 phases per location, interleaved, flip angle 90, delay after acquisition-minimum. Using a visual stimulus package, color photographs were presented in a mini-block design while neuroimaging was performed. In a typical session, after a 4 second lead-in time, a blank screen was displayed for 4 seconds, then the picture of interest for 4 seconds, and this was repeated for the scan time.

The fMRI scan volumes were motion-corrected and spatially smoothed in-plane, normalized and analyzed for neuroimaging activation using MedX, as described elsewhere (Marks et al., 2007a).

RESULTS

Out of 134 patients actively treated with interferon for HCV + RBV since 2004, eleven (8.2%) (Table 1)

patients developed SI (and / or HI) temporally related to use of IFN. One patient (#79) completed suicide, over 16 months after completing treatment with IFN.

Figure 2

Table 1: Patients with a history of SI temporally related to IFN

Patient ID	Sex	Age	Suicidal Ideation
131	M	57	Treated with non-peg IFN in past developed SI
96	M	53	Developed SI in the past while on Pegasys
95	F	39	Developed SI in the past while on Peg-Intron
247	M	26	Developed SI in the past while on Peg-Intron
288	F	37	Developed SI in the past while on Pegasys
79	M	40	Past IVDU, Anx and Dep but not SI while on IFN; completed suicide 1 yr after IFN
189	F	25	While on Peg-IFN, no change in baseline anger, HI, irritability, aggression
126	F	50	Developed SI while on Peg-Intron
291	M	57	Developed SI after first dose of Peg-Intron
403	F	54	Developed SI and HI while on Pegasys
446	F	37	Prior IVDU; SI, Anx Dep on IFN

SI = suicidal ideation HI = homicidal ideation Anx = anxiety
Dep = depression

IVDU = intravenous drug use

PATIENTS STUDIED WITH FMRI

Patient #288 is a 37 year old Caucasian female with HCV. She has a history of bipolar disorder, treated with Lithium and Zyprexa, a remote history of IVDU, alcohol use one year before treatment, and no past SI. On her 3rd week of treatment with IFN (Pegasys) + weight-based ribavirin (WBR), she required an acute psychiatric hospitalization for exacerbation of mania, with suicidal thought. With adjustment of her antipsychotic medication, her mania returned to baseline and her suicidal thoughts subsided. The IFN treatment was continued during this time, and she was imaged within 6 days after her 8th injection of IFN. Her starting viral load was 2,760,000, AST 229, and the viral load at 12 weeks was <10 (responder to treatment). Patient #288 was insistent that the manic episode and suicidal thoughts were causally related to the use of IFN. Further, this patient was easily identified (Table 2) by structured interview before treatment as belonging to an at-risk group for developing SI. Patient #288 exhibited a wide-ranging brain activation (Table 3) on fMRI while viewing some (depression #30 and homicide #1) but not all displayed photos. Most of the images caused no emotional arousal, but she did feel sorry for the persons depicted on one of the Depression and one of the Homicide images.

Patient #77 a 55 year old black male with HCV was imaged as a control. He has a remote history of SI (not temporally

related to IFN) but never had an actual suicide attempt. He related that, while viewing test images during fMRI sessions, most of the images caused no emotional arousal.

Figure 3

Table 2: Demographics and Risk Factors for SI

Patient ID	#77	#288
Age	54	37
Sex	M	F
Race	African American	Caucasian
IVDU		
Months on treatment	8	8
Illicit drug use	Cocaine	
SI	In the past, not temporally related to IFN	Temp related to IFN
History of childhood physical and/or sexual abuse	No	
H/O IVDU	No	1998
Alcohol use	Occasional	2006
CNS-active drugs	No	Lithium
Suicidal thoughts	Remote	Temporal to IFN use
Smoking	Yes	Yes
Hopelessness	Now, secondary to job loss	
BDS during (12 weeks) treatment with IFN	48 (severe)	32 (severe)
Initial Hep C Viral load	2,760,000	2,590,000
Previous H/O any psychiatric illness	Depression, anxiety	Manic depressive
H/O substance abuse	Cocaine 1995	Yes
H/O psych illness	No	
Interferon	Peg-IFN alpha 2a	Peg-IFN alpha 2a
IFN-related mood disorder	Possibly inc Depression, resolved off IFN	Suicidal thoughts
Viral response to treatment	Initial response, then breakthrough	Not yet determined

Data based upon pre-treatment (IFN) interview.
CNS-active drugs = amphetamine, cocaine, antidepressants, others
IVDU = intravenous drug abuse

After carefully reviewing the patients medical and psychiatric history (Table 2), it was determined using standard accepted methods of determining causation (Marks 2005) that IFN was at least probably (out of a range of unlikely, possible, probable and definite) the cause of the acute SI in patient #288. While patients occasionally have given reports while under treatment with IFN of the temporal development of anger, irritability and aggression, one patient (#403) who was treated with peg-IFN prior to 2004 also reported homicidal thoughts while receiving IFN. Another patient (#189) reported homicidal ideation, both off and on IFN, which was temporally related to use of SSRI medication.

Patients #77 and #288 underwent functional MR imaging, and were presented with the visual images in Figures 1-3.

Figure 4

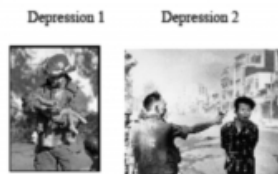
Figures 1. Visual Stimulation of Homicidal Ideation



Figures 2. Visual Stimulation of Suicidal Ideation



Figures 3. Visual Stimulation of Depression



Figures 1-3. Visual stimuli presented during functional MR imaging. Patient #288 responded most to images Homicide 1 and Depression 2, whereas patient #77 responded minimally to only images Suicide 2 and Depression 2.

Patient #288 (currently having SI) showed wide-ranging activation for two visual stimuli (D2 and H1) with violent content, whereas patient #77 (no recent SI, only minimal in the past) exhibited minimal brain activation with the same images. Neither patient showed brain activation in fMRI for the images of suicide, and they both related that the pictures of suicides did not evoke in them suicidal ideation.

Figure 5

Table 3: Brain activation during visual stimulation, sorted by intensity of activation per brain region.

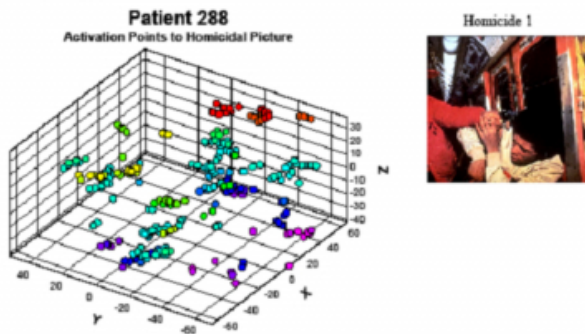
Lobe	Region	Subregion	Broadman	Intensity
L Frontal Lobe	Sub-Gyral	White Matter	*	31
L Temporal Lobe	Sub-Gyral	White Matter	*	23
R Temporal Lobe	Sub-Gyral	White Matter	*	18
L Temporal Lobe	Sub-Gyral	White Matter	*	15
R Temporal Lobe	Middle Temporal Gyrus	White Matter	*	13
L Temporal Lobe	Middle Temporal Gyrus	White Matter	*	10
R Frontal Lobe	Superior Frontal Gyrus	Gray Matter	9	10
R Sub-lobar	Extra-Nuclear	White Matter	*	10
L Frontal Lobe	Superior Frontal Gyrus	Gray Matter	9	9
L Sub-lobar	Thalamus	Gray Matter	Pulvinar	9
R Temporal Lobe	Superior Temporal Gyrus	White Matter	*	9
L Temporal Lobe	Middle Temporal Gyrus	Gray Matter	21	8
R Frontal Lobe	Superior Frontal Gyrus	White Matter	*	8
R Sub-lobar	Thalamus	Gray Matter	Pulvinar	8
L Frontal Lobe	Superior Frontal Gyrus	White Matter	*	7
R Frontal Lobe	Precentral Gyrus	White Matter	*	7
R Parietal Lobe	Inferior Parietal Lobule	White Matter	*	7
R Frontal Lobe	Middle Frontal Gyrus	White Matter	*	7
L Limbic Lobe	*	*	*	6
R Limbic Lobe	Parahippocampal Gyrus	White Matter	*	6

The activation points (Table 3) for Patient #288 were plotted as a scatter graph (Figure 4). Many areas of the brain showed activation in response to the presentation of certain (Homicide 1, Figure 1) but not all images.

Activation occurred particularly in the sub-gyral and medial temporal white matter.

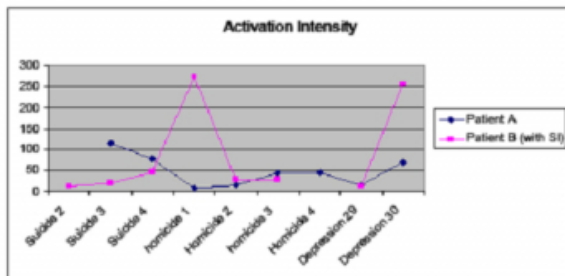
Figure 6

Figure 4. The activation points for activated voxels were graphed for patient #288, viewing Homicide 1, and shown as a scatter graph.



Patient #77 (Patient A) responded weakly (Figure 5) to the following images, and represented non-specific activation: Suicide 3 and Depression 2 (Depression 30). Patient #288 (Patient B) responded strongly with brain activation to two images: Homicide 1 and Depression 2 (Depression 30). This indicates that the visual stimulation was related to specific pictures or their related concepts, rather than to a general response.

Figure 5. Activation Intensity (# voxels) by Patient and by Visual Stimulation



Patient A = #77, Patient B = #288 Depression 29 and 30 = Depression 1 and 2 of Figure 3.

DISCUSSION

IFN are cytokines - biologic mediators that are used clinically in a wide spectrum of disease states, including cancer and infectious diseases such as viral hepatitis B and C. Interferon alpha 2 (IFN- α 2) is a specific cytokine produced by leukocytes upon viral infection, that can mediate a wide range of neuromodulatory properties in the central nervous system (CNS). Adverse effects which have been associated (PI) with IFN treatment include apathy, depression, fatigue, irritability, cognitive dysfunction, suicidal thoughts, and an exacerbation of drug seeking behavior (Meyers et al., 1991; Pavol et al., 1995; PI for PEG-IFN; Marks et al 2008 submitted). It is certainly understandable how a combination of these factors, in a vulnerable individual, could lead to development of SI. Low-dose IFN- α 2 therapy was associated at week 12 of treatment with significant dose-dependent prefrontal hypometabolism (Juengling et al., 2000), changes in the Beck (1988) Depression Inventory (part of our test battery), and was even found in clinically non-depressed patients. These findings may reflect a possible predisposing factor for - α 2 associated neuropsychiatric syndromes, and may contribute to a pathophysiological model of affective disorders, as endogenous - α 2 levels are elevated in a subset of psychotic

patients during acute disease. Changes in prefrontal cortical activity may in a sense be a surrogate for a "vulnerability factor" for the development of depressive symptomatology of patients treated with IFN- α 2.

Published data and the prescribing information (PI) for Pegasys and Peg-Intron indicate that IFN (and Rivabirin) dosages must be reduced in as many as 10-40% of patients and discontinued in 5-15% because of severe side effects from treatment. Although not all patients with HCV develop neuropsychiatric symptoms when treated with IFN, investigators have reported that between 10% and 40% of patients experience depressive symptoms. Overall, interferon dosage must be reduced in many patients and discontinued in as many as 40% of patients because of severe side effects, although these numbers are somewhat higher than observed in our own patient population.

Capuron et al., (2005) found that patients with HCV who were or were not treated with IFN showed similar task performance and activation of parietal and occipital brain regions using fMRI. Treatment with IFN in the Capuron study did seem to cause significant activation of the dorsal part of anterior cingulate cortex (ACC), although we did observe this for patient #288 in the current study. The activation of the ACC has been correlated with task-related errors, helping to understand cytokine-induced behavioral changes. A wide-ranging (left frontal subgyral, left and right temporal subgyral, R and L middle temporal gyral) activation of the brain was seen (Table 3) for patient #288, rather than just specific areas dealing with emotion (temporal area).

A number of medications have been causally related to the development of SI, including: Accutane (PI), amantadine (Shea), amphetamines, antiepileptics (Neurontin, Lyrica), Chantix (Kuehn), Interferon (Ademmer; PI), Reglan (Marks, 2007b), steroids and SSRI (PI). Recently (FDA Advisory Committee), reports of suicidal ideation have been reported for Zimulti (Sanofi-Aventis SA obesity pill in clinical trials). In our own series of 134 patients taking interferon for treatment hepatitis C, the majority did not seem to develop (on routine questioning) clinically significant depression, anxiety, SI or drug-craving. Further, one of the patients (#77) in this study had a past history of SI while not on IFN but did not develop recurrence of SI while taking IFN. One patient developed HI which was at least temporally associated with IFN use, and we hope to perform fMR imaging on this person. We are also aware of several of our patients, not treated with IFN, who reported developing

SI or HI whenever they were given a SSRI medication. Two patients (#97 and #288) developed an IFN-induced acute psychosis requiring discontinuation of IFN in one (#97), with resolution of the symptoms of psychosis. Patient #288 required psychiatric hospitalization for her symptoms of IFN-induced worsening of psychosis, which resolved on adjustment of antipsychotic medication, but did not require a dosage adjustment of IFN. To date, neither the psychosis nor SI has recurred, despite continuation of IFN treatment through 48 weeks.

Because we are at this time reporting on only two patients, it is possible that our results are coincidental. Although increasing the fMRI study sample size would lend additional support to the findings, the treating physician (DHM) has been reluctant to maintain patients on IFN who are acutely suicidal to allow for neuroimaging. Certainly, treating patients at risk for SI with a medication known to increase SI is not without its own obvious risks. The incidence of IFN-induced SI (9%) is slightly higher than previously reported (1.1%, Helbling et al., 2002) and certainly raises cause for concern and vigilance, but because of our small sample size, is not of statistical significance.

After extensive discussion with patient #288, there is no reason to think that the structured briefing before starting treatment concerning the potential to develop SI was responsible for causing SI. Nor could it be said that reminder at the regularly scheduled treatment appointments of the potential to develop SI resulted in an increase in SI.

Sublette et al (2006) presented neuroimaging findings that they felt were specific to bipolar disorder and suicide in at-risk youth. Among suicide attempters, after serotonin stimulation with fenuramine, high lethality of attempt was associated with hypofunction of the ventral, medial and lateral PFC, as visualized with [18F]-FDG PET (Oquendo et al., 2003). Further, the metabolic rate of glucose in the same regions was correlated with verbal fluency (Oquendo et al., 2003). These findings are consistent with a body of literature concerning the intersection between involvement of the serotonergic and noradrenergic systems and the ventromedial PFC in suicide (reviewed by Mann 2003). In our own study, we did not observe activation of the ventral, medial or lateral PFC of patient #288 with fMRI (Table 3). While we can not call this hypofunction, we did not observe hyperfunction of these regions.

The importance of brain serotonin in suicide has been demonstrated in multiple studies relating low cerebrospinal

fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid to severity of lifetime aggressivity, history of suicide attempts, lethality of past attempts, and future suicidal behavior (reviewed by Placidi et al.; Audenaert). A stress–diathesis model proposed for describing suicide risk in clinical and neurobiological terms suggests that hopelessness and impulsivity may be related to impaired serotonergic input into the ventromedial PFC (Mann 2003). In fact, Sublette et al propose using a profile of neurobiological markers to screen for bipolar disorder and suicide risk. They posit that this approach may provide for earlier and more accurate diagnosis, perhaps even in the pre- or subsyndromal stages in high-risk youth. We are actively looking at this also, and are considering implementing a standard protocol.

LIMITATIONS

Our data and conclusions for this brief report are limited because of the small number of participants, and the inferences drawn between thought and activation seen with fMRI. There is need for further study and replication with a larger series of subjects.

CONCLUSIONS

Even though this is preliminary data on a small number of subjects, several points are of interest. The incidence of IFN-induced SI, as was the case for IFN-induced depression, is very low in this treatment population and representative of the expected incidence rate for the population in general. We show how clinically significant medication-induced CNS effects (SI, depression, anxiety) can be detected using fMRI. Brain activation occurs for specific visual stimuli, and the pattern of brain activation in this case was wide ranging and involved many different areas of the brain, particularly the left frontal and temporal lobes, sub-gyral area, and the right cerebrum, temporal lobes, sub-gyral area. We note that the patient who did not develop clinical SI did also not develop activation of those areas of the brain known to respond to SI, correlating the specificity of results. Functional MR imaging has the potential to be of value in detecting sub-clinical CNS changes due to medication adverse effects that could increase the potential for suicidal thought. Such individuals may be at a higher risk of this fatal adverse effect, and would warrant withdrawal of IFN treatment.

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