Interferon-induced depressive illness in hep C patients responds to SSRI antidepressant treatments

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Abstract: This paper examines the role of selective serotonin reuptake inhibitors (SSRIs) in the treatment of hepatitis-C virus (HCV) patients who have developed interferon-α induced depression. A 2-year data analysis of HCV psychiatric liaison clinic has been undertaken. The diagnosis, treatment, and progress of those patients who were treated with interferon-α (INF-α) are reported. 53 of the 78 patients enrolled at the HCV Clinic and treated with INF-α were referred for psychiatric consultation. Six patients developed major depressive illness following INF therapy. They were all treated with SSRIs and they made full recovery. This is a significant observation and is concordant with other studies. Its biochemical ramifications are presented. It is concluded that INF-induced depression is fully reversible. A hypothesis is proposed that SSRIs modulate the neuro-protective neurotoxic ratio by possibly inhibiting the indole-2,3-dioxygenase induction of the kynurenine pathway.

Keywords: hepatitis-C virus (HCV), SSRIs, interferon-α, indole-2,3-dioxygenase, major depression

Introduction

Hepatitis C is a major public health problem, 170 million people were reported to be affected worldwide (WHO 1999), 225 000 in Australia (2002). The cytokine interferon alpha (INF-α) is administered in the treatment of hepatitis-C virus infection (HCV) for its immuno-protective quality. The HCV is an enveloped RNA virus and 50% of infections progress to chronicity and up to 70% of the asymptomatic carriers have chronic active hepatitis and or cirrhosis. HCV produces symptoms of major depression including fatigue, increased sleepiness, irritability, loss of appetite, and cognitive difficulties (Capuron et al 2001; Wichers and Maes 2002; Wichers et al 2005a). It has been hypothesized that major depressive illness in the general population is accompanied by activation of the inflammatory response system. An increased production and levels of pro-inflammatory cytokines by monocytes and Th-1 like lymphocytes, for example, interlukin-1β, IL-6, tumour necrosis factor-α (TNF-α), and INF-γ (Kronfol 2002), have been found in major depression occurring in the general population. Pro-inflammatory cytokines have been found to have significant effects on the tryptophan metabolism through the enzyme indoleamine-2,3-dioxygenase (IDO), which is activated. This results in diversion of tryptophan causing an increase in the ratio of neuro-protective kynurenate and neurotoxic–neurodegenerative quinolinate (Myint and Kim 2003). This cytokine–tryptophan interaction leading to an imbalance between quinolinate and kynnurate in the brain lies at the basis of the neurodegerative hypothesis of depression. In INF-α-induced depression intervention with selective serotonin reuptake inhibitors (SSRIs) ameliorates the symptoms (Mussulman et al 2001). This paper concerns the onset of major depression in a cohort of INF-α-induced depression in HCV patients and the

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clinical observation of complete recovery with SSRIs. Activity of IDO as the possible cause of IFN-α-induced depression is also discussed.

Methodology

We examined the role of SSRI antidepressant therapy in INF-α-induced depression in patients with HCV. The data were collected from the psychiatric liaison liver clinic of a large teaching hospital in Canberra. Treating specialists and nursing staff referred patients requiring psychiatric input. No formal screening tools were applied prior to psychiatric consultation. The main reasons for referrals were 1) identifying high risk cases to determine the suitability for combination INF-α and ribavirin treatment; 2) developing a comprehensive treatment plan with the liver clinic team in selected cases to maximize compliance for completion of therapy; and 3) for early detection and treatment of INF-α-induced neuropsychiatric complications particularly depression in order to achieve better treatment outcome. All patients were enrolled for HCV treatment as per the liver clinic protocol. A consultant psychiatrist examined the referred patients and the psychiatric diagnoses were based on the DSM-IV criteria. Treatment outcome was measured as an achievement of remission symptoms of major depression.

Results

A total of 78 patients were assessed and found eligible for INF-α treatment by the gastroenterology team in their Hep C clinic. Of these, 53 patients were referred for psychiatric consultation. The mean age of the cohort was 40 years and males represented 62.8% of the sample. The mean duration of HCV was 11.79 years. Five of these patients developed an aggravation of personality disorder NOS (DSM-IV) without co-morbid depression. One patient developed severe neurotoxicity and another one developed psychosis. Six of the 53 patients developed major depressive illness following the INF-α treatment and had no other psychiatric co-morbidity. Six patients who developed major depression and 5 who had aggravation of personality disorder were treated with SSRI antidepressants and their progress was recorded fortnightly. All the six patients who developed depression after the INF- treatment achieved full remission. Four of these patients completed the full course of INF and ribavirin treatment for a period of 6–12 months, 1 patient developed liver cell carcinoma, and 1 dropped out in spite of good remission before completing the antiviral therapy. Table 1 provides more details of these six patients. The five patients who had aggravation of their personality disorder and received the antidepressants showed no improvement in their mental state.

Discussion

The total number of patients observed in this study is small, as is also the case with other similar reports of patients of major depressive illness secondary to INF administration in HCV patients. These studies are not standardized and do not take into account dose and duration of INF treatment. Inevitably they also have heterogeneous patient populations, and there is non-uniformity of the diagnostic criteria for depression and the assessment methods employed.

In the six patients who developed significant depressive illness, the complete therapeutic response to SSRI antidepressant therapy in all of them is striking. Other workers have also reported similar high success rates in the treatment of depression following INF- therapy, with Turner and Blackwell (2005) reporting effective response in up to 75% and Lang et al 78.5% (2003). Both Schramm et al

Table 1 IFN-induced MDD and treatment outcome

Age and sex (years)	Onset of MDD following IFN-α therapy (weeks)	ADT	ADT duration (months)	Outcome 1[a]	Outcome 2[b]
44 M	4	Paroxetine 40 mg	12/12	Full	Yes
52 F	6	Paroxetine 40 mg	14/12	Full	Yes
35 M	6	Citalopram 20 mg	10/12	Full	Yes
55 F	6	Sertraline 50 mg	8/12	Full	No, treatment stopped due to liver carcinoma
22 F	10	Sertraline 50 mg	3/12	Full	No, dropped out
38 M	16	Sertraline 50 mg	2/12	Full	Yes

[a]Outcome 1 = remission of MDD
[b]Outcome 2 = completion of antiviral treatment
Abbreviations: ADT, antidepressant treatment; INF, interferon; MDD, major depressive disorder.

(2000) and Hauser (2004) also reported almost 100% success in their series. This is in contrast to the treatment outcome in randomized, controlled clinical trials in major depression in the general population where the overall efficacy for most old and new antidepressant treatments is 50%–55% (Parker 2005; Khan et al 2005). We would like to take into account the statistical differences between very small numbers of patients observed in this study with the outcome of much larger clinical studies. Nonetheless, differences in the reversibility of INF-induced depression pending its further confirmation from larger standardized studies is a significant clinical observation. This observation warrants further discussion. If the pathophysiology of INF-α is significantly reversible then there is cause to believe that this pathophysiology differs from that of major depression occurring in the general population. The role of intrinsic cytokines may incorporate several other and more complex pathways (Wichers and Maes 2002) in major depressive disorder. For example, intrinsic cytokines are potent modulators of corticotrophin-releasing hormone (CRH) which produces heightened hypothalamic-pituitary-adrenal (HPA) axis activity characterized by an increase in adrenocorticotropic hormone and cortisol, both of which have been reported to be elevated in major depressive illness (Brebner et al 2000; Dunn 2001).

The role of the enzyme IDO has been implicated in the pathophysiology of depression induced by INF-α in HCV patients (Wichers et al 2005b). This enzyme is stimulated by proinflammatory cytokines including INF-α (Wichers et al 2005b). Its implications are as follows. First, the stimulation of IDO activity induces the kynurenine pathway resulting in the production of neurotoxic metabolites (depressogenic event). Second, the tryptophan availability to brain is decreased. In a prospective study of 16 patients with hep C who were treated with INF-α, Wichers et al (2005b) measured the onset and severity of depression, tryptophan, and kynurenine ratio and its metabolic product kynurenic acid ratio. They found that the Montgomery Asberg Depression Rating Scale was significantly associated over time with the kynurenine and kynurenic acid ratio, reflecting increased IDO activity. The Wichers et al (2005b) study favours the IDO switch pathway rather than the serotonin depletion.

We speculate that one possible or an alternative mechanism for the reversibility and complete remission of symptoms in these patients may be explained by the down-regulation/modification of the IDO stimulation/activity, with SSRI antidepressants resulting in modulation of the kynurenate and the quinolinate ratio. This speculation is further supported by the observation that in our cohort, the patients who received INF-α therapy and developed aggravation of their personality disorder, showed no improvement, as they possibly did not have the underlying IDO pathophysiology and therefore INF-induced depression.

Conclusion

The SSRIs have therapeutic efficacy in the treatment of INF-α-induced major depression in HCV patients and may have mechanism and sites of action other than conventionally considered. Other implication of our observation are that patients who are receiving treatment with pro-inflammatory cytokines should be routinely screened for depressive symptoms, as these symptoms appear to be fully responsive to therapeutic intervention. Future clinical studies of antidepressants should incorporate cellular and biochemical response of the monocytes and lymphocytes in a variously depressed population of patients. A consensus should be developed as how to undertake larger multicenter studies to examine the role of IDO, in the pathophysiology of depression.

Acknowledgments

The authors thankfully acknowledge the constructive suggestions of Daniel and Pal, the Gupta boys, through the earlier drafts of this manuscript.

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