LETTERS

Does antidepressant medication in patients with hepatitis C undergoing interferon α treatment reduce therapeutic efficacy?

Activation of the inflammatory immune system, as evidenced by the effects of interferon α (IFN α) treatment, induces depressive symptoms. Prescription of a selective serotonin reuptake inhibitor (SSRI) is now advocated in combination with antiviral therapy in patients exposed to IFN α when early symptoms of depression emerge. The recently published article written by Kraus *et al* (*Gut* 2008;**57**:531–6) gives further evidence for the efficacy of SSRIs to treat depressive symptoms during IFN α treatment.

The mechanisms by which SSRIs reduce depressive symptoms remain unclear. Several hypotheses, such as impact on serotonin activity or neurotrophic actions, have been proposed. Another, that has good face validity in this context, is that the anti-inflammatory properties of SSRIs mediate at least in part the decrease in depressive symptoms. Antidepressants have been shown in animals and humans to inhibit the production and/or release of proinflammatory cytokines and to stimulate the production of anti-inflammatory cytokines (such as interleukin 10). In addition, recent data demonstrate that antidepressant-like effects of desimipramine in the forced swimming test (an animal model frequently used to evaluate antidepressant efficacy) depend on the ability of the drug to inhibit central nervous system production of tumour necrosis factor α .¹

Given the facts that (1) activation of the inflammatory immune system is responsible for increased antiviral activity and the development of depressive symptoms, (2) SSRIs reduce depressive symptoms during IFN α treatment and display anti-inflammatory effects, the hypothesis may be proposed that, whilst effectively reducing depressive symptoms, SSRIs may simultaneously reduce the efficacy of the treatment against hepatitis C virus (HCV), by reducing inflammatory activity. Based on this theory, the following two premises should apply. First, patients showing a good response to antiviral treatment have increased Th-1 cell activation and increased risk for depressive symptoms. Secondly, SSRIs, by reducing Th-1 cell activation, reduce both depressive symptoms and the probability of viral clearance.

With regard to the first premise, described above, few studies have been published reporting data on the association between viral clearance and depressive symptoms. Loftis and colleagues² found that IFN α response rates (both end-of-treatment

response (ETR) and sustained viral response (SVR)) were significantly higher in those patients who developed depression during treatment than in those who did not (ETR, 61.5% (8/13) and SVR, 38.5% (5/13) vs ETR, 26.9% (7/26) and SVR, 11.5% (3/26), respectively). Raison and colleagues,³ however, showed an association in the opposite direction: the lower the increase in depressive symptoms as measured with the Zung self-rating scale, the higher the probability of viral clearance. Two other studies found no associations. In order to resolve this apparent discrepancy, we analysed data from an IFN α -treated HCV patient sample, previously described in Wichers *et al*,⁴ in order to examine the association, using regression analysis, between alanine aminotransferase (ALAT) values and depressive symptoms. Increased ALAT values indicate the presence of an infected liver, and ALAT response to treatment is known to correlate strongly with a decrease in or negativity of HCV RNA. The results showed that increased response to treatment (as indicated by a decrease in ALAT) predicted an increase in depressive symptoms ($B = -0.090$, $p < 0.001$).

Concerning the second premise, no study designed to examine whether SSRIs impact negatively on the probability of viral clearance during IFN α treatment has been performed. One study that does give some information about this association shows that the SSRI group had less viral clearance than the placebo group, although numbers were very small.⁵

We conclude that although there are strong theoretical considerations that support the possibility that SSRI treatment may negatively influence viral clearance in IFN α -treated patients, this assumption has not been investigated. There is an urgent need for studies designed and powered to examine this hypothesis.

G Robaey, M C Wichers,² J De Bie,³ G H Koek,⁴ F Buntinx,^{5,6} J Van Os^{2,7}

¹ Department of Gastroenterology and Hepatology, Ziekenhuis Oost Limburg, Genk, Belgium; ² Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, The Netherlands; ³ Department of Psychiatry, Ziekenhuis Oost Limburg, Genk, Belgium; ⁴ Department of Internal Medicine, Section of Gastroenterology and Hepatology, Academic Hospital Maastricht (AZM), The Netherlands; ⁵ Department of General Practice, Katholieke Universiteit Leuven, Leuven, Belgium; ⁶ Department of General Practice, Maastricht University, Maastricht, The Netherlands; ⁷ Division of Psychological Medicine, Institute of Psychiatry, London, UK

Correspondence to: Dr M C Wichers, Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, The Netherlands; m.wichers@sp.unimaas.nl

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Authors' response

In their letter, Robaey *et al* refer to our study¹ on the antidepressant treatment of interferon (IFN)-induced depression in patients with chronic hepatitis C virus (HCV) infection.

We fully agree with the authors' statements that (1) prescription of a selective serotonin reuptake inhibitor (SSRI) is indicated and highly effective¹ when clinically relevant symptoms of depression emerge and (2) the exact mechanisms by which SSRIs reduce depression in these patients are still unclear. Nevertheless, with respect to the latter point, we would like to emphasise that there is considerable evidence for the serotonin pathway as an important candidate to confer both the development of IFN-induced depression and its reduction by the use of SSRI-type antidepressants. In a recently published paper,² we could demonstrate that both the incidence and severity of IFN-induced depression are significantly associated with an allelic variation in the 5-hydroxytryptamine 1A (5-HT_{1A}) receptor gene (*HTR1A* polymorphism).

The issue of a putative association between the degree of IFN-induced depression and the outcome of antiviral IFN-based treatment has repeatedly been raised in the recent literature, and has produced differing or even contradictory results. In addition to the references given by Robaey and co-workers, we would like to mention a study published by us in 2007,³ where we found no statistically or clinically significant relationship between the incidence or extent of IFN-induced depressive symptoms and therapy outcome (in terms of sustained virological response (SVR)). This was a prospective longitudinal study including 101 therapy-naïve HCV outpatients who received a combination therapy with peginterferon alfa-2b and ribavirin, and whose neuropsychiatric symptoms were monitored in a repeated-measures design (Hospital Anxiety and Depression Scale, DSM-IV criteria for major depression).