Course of Depression During the Initiation of Interferon Beta-1a Treatment for Multiple Sclerosis

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Objective: To examine the hypothesis that increases in depression after initiation of treatment with interferon beta-1a for multiple sclerosis can be explained as representing a return to pretreatment levels of depression.

Design: Level of depression in patients with multiple sclerosis was assessed at 3 time points: 2 weeks before initiation of interferon beta-1a treatment, at initiation of treatment, and at 2-month follow-up.

Setting: A health maintenance organization.

Patients: Fifty-six patients with confirmed relapsing forms of multiple sclerosis.

Main Outcome Measure: The depression-dejection scale of the Profile of Mood States.

Results: Patients who scored high on the depression measure 2 weeks before the initiation of interferon beta-1a treatment showed significant reduction in depression at the initiation of treatment. However, depression returned nearly to initial levels within 2 months.

Conclusions: These findings suggest that increases in depression after initiation of interferon beta-1a treatment are related to level of depression 2 weeks before initiation of treatment. Physicians should assess history of depression for all patients in whom interferon beta-1a treatment is initiated. Patients with a recent history of depression are at risk for increased depression within 2 months after starting interferon beta-1a treatment, even though they may not be depressed at the time of treatment initiation.

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INTERFERON beta-1a is approved by the Food and Drug Administration for treatment of patients with relapsing forms of multiple sclerosis (MS). Interferon beta-1a is well tolerated. Only 4% of the actively treated patients in an interferon beta-1a phase 3 clinical trial discontinued injections because of adverse effects. In clinical practice, 11% discontinue within 4 months of initiating treatment.

Depression has been reported to increase during the first 2 to 6 months of treatment in clinical settings with both interferon beta-1b and interferon beta-1a. While it is possible that these drugs induce depression, it is also possible that patients’ therapeutic expectations result in a temporary reduction in depression at the initiation of treatment. In this case, the observed increase in depression could, in fact, reflect a return to baseline level of depression.

This study examined the hypothesis that increases in depression associated with interferon beta-1a can be explained as representing a return to pretreatment levels of depression.

RESULTS

PATIENT CHARACTERISTICS

Two patients were excluded because they met criteria for dementia, while 7 patients either discontinued interferon beta-1a treatment or were unavailable for follow-up. This left 56 patients who were enrolled in the study. The mean ± SD age of the patients was 43.3 ± 9.5 years; 47 (84%) were women and 9 (16%) were men; 38 (68%) were married or living with a significant other, 11 (20%) were single, 5 (9%) were separated or divorced, and 2 (4%) were widowed; 30 (54%) were employed, 21 (38%) were unemployed or receiving disability benefits, and 5 (9%) indicated they were otherwise engaged (student, homemaker, and/or parent). The mean ± SD GNDS score was 12.9 ± 8.16. According to the GNDS interview, 8 patients (14%) had no gait disturbance, 34


**PATIENTS AND METHODS**

The subjects were 65 sequential patients with confirmed diagnoses of MS, who were approved by Kaiser Permanente Medical Care Program of Northern California's utilization review to initiate interferon beta-1a. Diagnosis was confirmed by chart review performed by a panel of 4 neurologists. Patients who met the criteria for dementia described below were excluded, as their responses to interview questions may not be valid.

Applications by treating neurologists for treatment of MS with interferon beta-1a were reviewed by a Kaiser Permanente Medical Care Program of Northern California utilization review board. Patients approved by the board were contacted by study personnel and informed consent was obtained. Patients were assessed by telephone 2 weeks before the initiation of interferon beta-1a treatment (time 1), within 2 days before the initiation of treatment (time 2), and 8 weeks after the initiation of treatment (time 3). Adherence to medication was measured by patient self-report and confirmed by pharmacy reports that the medication had been received by the patient.

Patients were assessed by telephone by means of the following instruments. The Profile of Mood States depression-dejection scale was used to assess depression. This measure, consisting of 15 adjectives rated on a 5-point Likert scale, has a potential range of 0 to 60.

Guy's Neurological Disability Scale (GNDS) is a brief structured interview that assesses 12 areas of functioning. The GNDS has a potential range of 0 to 72. It has been shown to have good reliability (α = .87) and is correlated with the Expanded Disability Status Scale. The GNDS was selected because it has been administered over the telephone.

The Neuropsychological Screen for Dementia Short Word List is a list-learning task consisting of 3 administrations of a 10-word list. The 12-minute delayed-recall (Short-D) was used as the measure of cognitive impairment. The Short-D has been shown to assess cognitive impairment in MS. Neuropsychological assessment by means of list-learning tasks has been validated for telephone administration.

Patients who scored below the fifth percentile were excluded from the study.

The data were analyzed by repeated-measures analysis of variance. (61%) had some gait disturbance but walked without aids, 10 (18%) used aids to walk, and 4 (7%) usually used a wheelchair to travel 22.5 m (25 yd). Patients had been diagnosed an average of 6.8 years before beginning treatment, with a range of 3 months to 28.7 years. No patients were in treatment for depression during the course of this study.

Time 1 depression was unrelated to sex, age, time since diagnosis, neuropsychological functioning, or marital status (all \(P>.36\)). Time 1 depression was related to the GNDS disability score (\(r = 0.42, P = .001\)) and to employment status, with patients unemployed (mean score, 21.5) or receiving disability benefits (mean score, 17.2) being significantly more depressed than those who were employed (mean score, 8.1; \(P = .007\)).

**ANALYSIS 1**

Level of depression varied significantly across time (\(F_{2,110} = 6.64, P = .002\)). The mean ± SD level of depression at time 1 (2 weeks before the start of interferon beta-1a treatment) was 12.2 ± 10.24; at time 2 (initiation of interferon beta-1a treatment), depression score was 7.8 ± 8.38; and at time 3 (8-week follow-up), depression score was 11.5 ± 10.54. Newman-Keuls post hoc analysis showed that depression at time 1 and time 3 was significantly higher than at time 2 (\(P = .003\) and \(P = .005\), respectively). Depression at time 1 was not significantly different from depression at time 3 (\(P = .59\)).

**ANALYSIS 2**

To examine whether the course of depression before and after initiation of interferon beta-1a treatment varied as a function of initial level of depression, patients were divided into depressed and nondepressed groups by means of a median split (median, 10) on the time 1 depression scores. This variable was called level of depression. A 2-way repeated-measures analysis of variance was performed with the use of level of depression as one factor and time (Profile of Mood States depression scores across times 1 through 3) as the repeated measure. As shown in the Figure, there was a significant effect for both level of depression (\(F_{1,54} = 35.8, P < .001\)) and time (\(F_{2,108} = 7.71, P = .001\)). There was also a significant interaction effect (\(F_{2,108} = 9.97, P = .001\)), indicating that the course of depression varied as a function of level of depression before the initiation of interferon beta-1a treatment. Newman-Keuls post hoc tests showed that level of depression in the nondepressed group did not change over time (all \(P > .49\)). Among the depressed group, level of depression at time 1 and time 3 was significantly higher than at time 2 (\(P = .001\) and \(P = .001\), respectively) but differed from each other only marginally (\(P = .05\)).
These findings indicate that initiation of interferon beta-1a treatment in patients with MS can temporarily affect the course of depression. Depressed patients showed a significant decline in their level of depression during the 2 weeks before initiation of interferon beta-1a treatment. However, within 8 weeks these patients' depression had returned almost to preinitiation levels. Level of depression in nondepressed patients remained unchanged through the course of initiation of medication. Thus, the hypothesis that increases in depression after the initiation of interferon beta-1a treatment are related to pretreatment levels of depression was supported. It should be noted, however, that the possibility that the medication may also contribute to depression in patients at risk for depression cannot be ruled out.

To date, there have been no reports on the assessment of depression as a side effect in controlled clinical trials of disease-modifying medications for MS. Several uncontrolled trials have reported increases in depression after the initiation of treatment with interferon beta-1b and interferon beta-1a. These studies argue that depression should be assessed in future clinical trials by means of standardized instruments. This study suggests that such assessment should begin at least 2 weeks before the initiation of the study drug.

These findings have important consequences for the clinical use of interferon beta-1a. Physicians are likely to see increases in depression among many patients in the first months of treatment with interferon beta-1a. Although patients may attribute this depression to the medication, these findings suggest that increases in depression more likely reflect pretreatment levels of depression. These findings suggest that physicians prescribing interferon beta-1a should assess the patient's history of depression, regardless of the patient's current mental status. Patients with a recent history of depressive symptoms can be expected to have those symptoms return in the first 2 months of treatment. Depression should be monitored closely in those patients, as depression in MS has been shown to be highly responsive to both psychotherapy and medications.

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