Disease-modifying therapy improved depression symptoms in multiple sclerosis patients: the POSIDONIA study

E. Montanari[1], M. Conti[2], D. Maimone[3], V. Torri Clerici[4], K. Plewnia[5], M. Frigo[6], A. Francia[7], A. Pala[8], A. Veneziano[9], POSIDONIA Study Group

[1]U.O. di Neurologia, Ospedale di Fidenza, Fidenza, [2]USSD Neuroimmunologia SM, Ospedale Papa Giovanni XXIII, Bergamo, [3]U.O. Neurologia, Ospedale Garibaldi - Nesima, Catania, [4]Centro Sclerosi Multipla - U.O. Neurologia 4, Fondazione Istituto Neurologico Carlo Besta, Milano, [5]U.O. Neurologia, Ospedale Misericordia di Grosseto, Grosseto, [6]Ambulatorio Neuroimmunologia Clinica Neurologica, Ospedale San Gerardo, Monza, [7]Centro Sclerosi Multipla, Azienda Policlinico Umberto I, Roma, [8]U.O. di Neurologia Ospedaliera, Presidio Ospedaliero A. Segni, Ozieri, [9]Medical Department, Teva Italia S.r.l., Assago, Italy

1. INTRODUCTION AND PURPOSE

Multiple sclerosis (MS) is a chronic, potentially highly disabling condition [1], and has a significant impact on health-related quality of life (HR-QOL) [1]. The unpredictable variations in symptoms, severity and progression of the disease may contribute to anxiety and depression in patients with MS. Medication use may reduce uncertainty and distress as patients may feel they are doing something to control the progression of their disease.

POSIDONIA (Prospective, Observational Study evaluating Impact of DMT treatment On the emotioNal burden in recently dIAgnosed multiple sclerosis patients) was a 12-month, prospective observational study that aimed to evaluate the impact of disease-modifying treatment (DMT) on feelings of anxiety and depression in patients with recently-diagnosed MS.

2. METHODS

Patients: The POSIDONIA study was conducted in patients diagnosed with MS (defined by revised McDonald criteria [2], who were willing to be treated with DMT, following clinical practice, with relapsing-remitting disease course, aged 18–65 years and had initiated DMT at the investigator's decision. Patients who had had any previous treatment with any DMT were excluded.

Study design: This study was conducted in approximately 40 centres in Italy. The decision to utilise DMT was made by the treating physician. Data were collected at baseline and at two follow-up visits at 6 months [visit 2] and 12 months [visit 3].

A total of 250 patients were enrolled, of whom 222 (88.8%) completed the study and comprise the per-protocol population. Approximately three-quarters of the patients were women (74.4%). Mean age and ages of first MS symptoms, MS diagnosis and MS exacerbation of 36.41, 33.31, 35.49 and 35.94, respectively (Table 1). Patients were at a very initial disease stage with mild symptoms. Baseline characteristics were similar between women and men, although there was a trend for younger age of disease onset in women (mean age at diagnosis of 34.84 years in women and 37.38 years in men; p = 0.064). At baseline, the mean HADS total score (12.27 ± 6.10 vs. 9.94 ± 5.21; p = 0.007) and the mean HADS-A score (6.20 ± 3.99 vs. 4.22 ± 3.41; p = 0.007) was statistically significantly higher in women than in men. Expanded Disability Status Scale (EDSS) scores had a mean of 1.58 at baseline and remained stable over the course of the study. All patients started treatment with a single DMT. Approximately half of the patients received glatiramer acetate (47.2%) and approximately half received interferon-β (51.2%). The majority of patients received DMT without modification during the study.

Table 1. Baseline demographic and disease characteristics

Characteristic	
Gender, n (%) [n=250]	
Female	186 (74.4)
Male	64 (25.6)
Age, years [n=250]	
Mean (SD)	36.41 (9.43)
Median (range)	36.00 (18.00–60.00)
Age at first MS symptom, years [n=245]	
Mean (SD)	33.31 (9.07)
Median (range)	31.74 (16.68–58.71)
Age at MS diagnosis [n=249]	
Mean (SD)	35.49 (9.48)
Median (range)	34.87 (17.81–58.98)
Age at last MS exacerbation [n=235]	
Mean (SD)	35.94 (9.26)
Median (range)	35.73 (17.87–58.71)
EDSS total score [n = 244]	
Mean (SD)	1.58 (1.06)
Median (range)	1.50 (0.00–5.50)
Mild disability (EDSS 0–4.5), n	242
Moderate disability (EDSS 5.0–6.5), n	2

EDSS = Expanded Disability Status Scale; MS = multiple sclerosis

Patient-reported outcomes: Three outcomes were considered. The first utilized the Hospital Anxiety and Depression Scale (HADS), looking at HADS anxiety (HADS-A) and depression (HADS-D) subscale scores, which range from 0 (no symptoms) to 21 (most severe symptoms). A HADS-A and HADS-D score of ≥8 indicates a high risk of anxiety and depressive disorder in MS patients [16]. The Short-Form 36 Health Survey (SF-36) assessed physical and mental health; scores range from 0 (poor health) to 100 (optimal health). The third tool was the Impact of Event Scale – Revised (IES-R), measuring impact of psychological stress of having MS. Healthcare provider-reported outcomes were assessed using the Hamilton Depression Rating Scale HDRS-17; a total score of 0–7 is considered normal, while ≥18 indicates substantial depression.

The primary study objective was change from baseline in anxiety and depression over 12 months, assessed by HADS. Secondary objectives were changes in depression, assessed by HDRS, HRQoL, assessed by SF-36, and disease-related psychological distress, assessed by IES-R scores.

Study conduct: All study participants provided written informed consent. The study adhered to the Declaration of Helsinki and to International Guidelines for Ethical Review of Epidemiological Studies; it was conducted in accordance with national/local laws/regulations. The study protocol was approved by the Independent Ethics Committee at each participating site. The study was sponsored by Teva Italia.

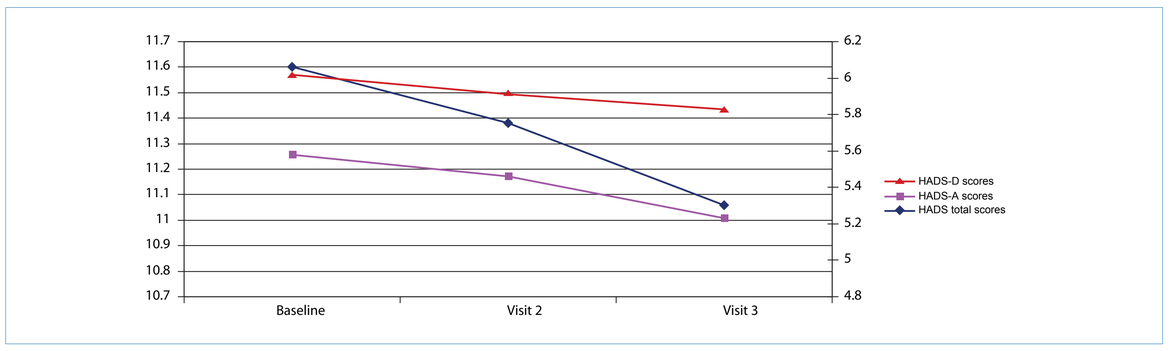
Statistical analysis: Unless otherwise stated, patients with missing data were not considered in the calculations. For analysis of the primary and main secondary endpoint, where >50% of (sub)total rating scale values were complete, the remaining missing values were calculated as the mean of the completed items. Missing (sub)totals of the rating scale owing to a non-monotonic pattern (i.e. data only present at visit 1 and 3) were determined by interpolation. SAS software was used.

3. RESULTS

Primary objective. At baseline, mean HADS total and HADS-A and HADS-D subscale scores were within the normal range (means of 11.60, m5.58 and 6.02, respectively). More importantly, there were no significant changes over time in mean HADS total and HADS-A and HADS-D subscale scores (Figure 1). No significant interaction between changes in HADS scores over time and for the two main types of DMT (glatiramer acetate and interferon-β) was found (p = 0.1677).

Exploratory analysis revealed that patients with baseline scores indicative of anxiety or depression (HADS total score of ≥16 [n = 46], HADS-A subscale score of ≥8 [n = 55] or HADS-D subscale score of ≥8 [n = 46]) tended to improve over time (Figure 2a).

Figure 1: Impact of DMT on patients' HADS scores



Right hand axis for HADS total score , whereas left hand axis concerns subscales HADS A and D.*) p-value between baseline, visit 2 and 3 of p<0.5050; 0.5063 and 0.6903, for HADS, HADS-A and HADS-D respectively

Patients with baseline scores in the normal range (HADS <16, HADS-A <8 or HADS-D <8 tended to worsen over time (Figure 2b). All 3 scales time-by-group interactions were statistically significant (p < 0.0001).

Figure 2a: Patients with anxiety or depression tended to improve (n=46)†

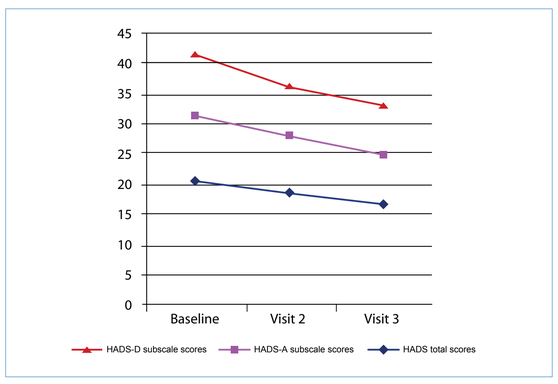
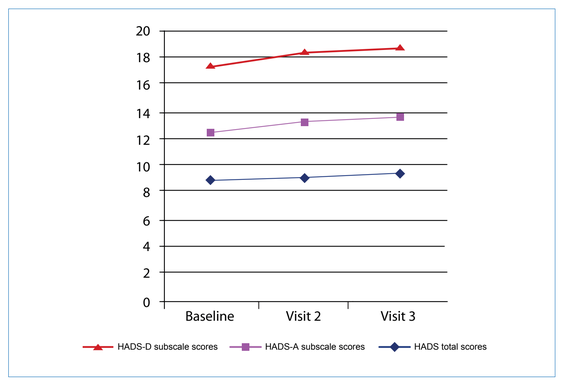


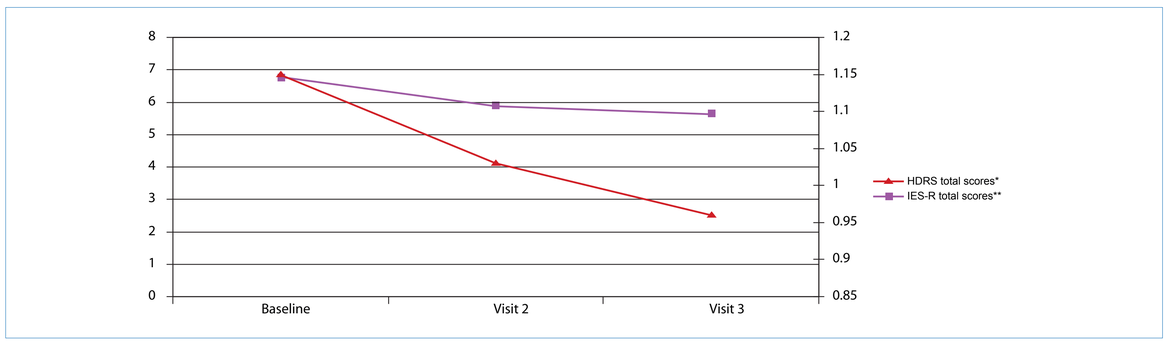
Figure 2b: Patients within normal range for anxiety or depression tended to worsen (n=155)



† high/normal refers to HADS total score of ≥16 and <16 (n = 46/155), HADS-A and -D subscale score of <8 and <8. All differences significant p<0.0001

Secondary objectives: Both the HDRS and IES-R total scores improved over time, with significant differences seen between all times, between baseline and visit 2 and between baseline and visit 3 (Figure 3). Changes over time in the SF-36 mental health domain were of borderline statistical significance (p = 0.0682).

Figure 3: Impact of DMT on patients' HDRS (depression) and IES-R (psychological distress) scores



Left hand axis for HDRS and right hand axis concerns IES-R

4. CONCLUSIONS

The current study extends the limited data to date concerning the effect of DMT on emotional burden in patients with recently-diagnosed MS. While there has been concern that immunomodulatory treatment may induce depression [3], studies have failed to demonstrate an association between interferon-β or glatiramer acetate and depression [3]. Data from the current study suggest DMT may improve symptoms of depression and anxiety.

- HADS total and HADS-A and HADS-D subscale scores did not significantly change over time. These results could be explained by the fact that HADS scale was developed as a screening instrument and may not be suitable to detect changes over time when symptoms at the baseline are very mild.
- Exploratory analyses suggested that patients with HADS scores indicating the presence of anxiety or depression at baseline did improve following the introduction of DMT, but patients with normal baseline scores worsened over time.
- Moreover, significant improvements were seen over time in HDRS total scores and IES-R total scores.
- No significant changes over time were seen in SF-36 domain scores; the change in the mental health domain score was of borderline statistical significance.

In summary, initiating DMT appeared to have a positive effect on emotional burden in patients with recently-diagnosed MS, with particular benefit to patients with anxiety or depression at baseline.

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CONFLICT OF INTEREST

E. Montanari has been involved in activities sponsored by Biogen Idec , Merck Serono, Novartis, Sanofi-Genzyme, Teva; M. Conti has been involved in clinical trials sponsored by Merck Serono, Novartis, Bayer, Biogen, Idec; D. Maimone has received speaker honoraria and travel grants from Bayer, Biogen Idec, Merck, Serono, Novartis, Sanofi Genzyme, and Teva; M. Frigo has been involved in Advisory Boards organized by Biogen Idec and Novartis and in clinical trials sponsored by Teva, Merck Serono and Almirall; A. Francia has been involved in activities sponsored by Teva, Novartis, Biogen Idec, Sanofi, Genzyme; A. Veneziano is an employee of Teva Italia S.r.l. All the other authors have nothing to disclose.