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ORIGINAL RESEARCH

Real-World 24-Month Outcomes of Ofatumumab in Relapsing Multiple Sclerosis: Efficacy, Safety, and the Impact of Frailty

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ABSTRACT

Introduction: Ofatumumab (OFA) is a highly effective therapeutic option for multiple sclerosis (MS), but real-world data on its efficacy and safety remain limited. We evaluated the real-world efficacy and safety of OFA in patients with MS and explored the predictive value of frailty.

Methods: We retrospectively collected clinical and MRI data from 12 MS centers in Central Italy, including patients who initiated OFA between April 2022 and January 2024. We

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assessed annualized relapse rate (ARR), clinical relapses, radiological activity, and safety. Frailty, defined as increased vulnerability due to age-related health deficits, was measured using a frailty index (FI). The study was approved by the local Ethics Committee (No. 6357).

Results: A total of 242 patients with MS were included (66.8% female and 33.2% male; mean age: 38.9 ± 10.3 years; disease duration: 7.7 ± 7.6 years). Of these, 95 (39.2%) were treatment-naïve, and 147 (60.8%) had switched from another therapy, mostly a first switch. The mean follow-up was 15.4 ± 5.4 months; all patients completed 12-month follow-up, and 103 completed 24 months. ARR dropped from 0.9 to 0.02 ($p < 0.001$). Only 4 patients (1.6%) had a clinical relapse, all within 6 months (mean time: 3.0 ± 1.8 months). Expanded Disability Status Scale (EDSS) scores remained stable ($p > 0.05$). MRI activity occurred in 10 patients (4.1%) at 6 months and 3 (1.2%) at 12 months; none at 24 months. Adverse events included flu-like symptoms (34.3%), injection site reactions (8.2%), and infections (18.5%). Among 239 patients assessed for frailty (mean FI: 0.06 ± 0.08), 187 were relatively fit (FI ≤ 0.10), 30 least fit, and 22 frail. FI predicted 24-month confirmed disability progression ($p = 0.0068$), with significant variation by frailty level ($p = 0.0009$).

Conclusion: This real-world study suggests that OFA is effective and safe for MS, offering rapid disease control. Lower frailty levels suggest preferential use in patients with lower baseline disability. Further large-scale, long-term studies are needed.

Keywords: Ofatumumab; Real-world study; Frailty; Effectiveness; Safety; Confirmed disability progression

Key Summary Points

Why carry out this study?

Multiple sclerosis (MS) is a chronic, disabling disease associated with a substantial personal and healthcare burden; despite its high efficacy, real-world data on ofatumumab (OFA) remain scarce.

There is a clinical need to understand how frailty—an age-related vulnerability state—may impact treatment outcomes in MS, particularly in real-world settings.

This study investigated the real-world efficacy and safety of OFA in patients with MS and explored whether frailty could predict disability progression.

What was learned from the study?

OFA real-world clinical settings markedly reduced relapse rates (ARR from 0.9 to 0.02) and MRI activity, with a low incidence of clinical relapses (1.6%) and stable disability scores over a mean follow-up of 15 months.

Frailty, measured via a frailty index, was a significant predictor of 24-month disability progression, highlighting the importance of incorporating frailty assessment into treatment planning and future clinical research.

INTRODUCTION

Multiple sclerosis (MS) is a chronic and progressive neurological disease characterized by neuroinflammation, demyelination, and neurodegeneration, which occur from the earliest phases of the disease [1]. Patients with MS accumulate disability through relapse-associated worsening or progression independent of relapse activity [2]. Early intervention with high-efficacy disease-modifying therapies (DMTs) may represent the best treatment approach to delay irreversible central nervous system damage and MS-related disability progression [3–5]. In this context, monoclonal antibodies targeting the CD20 molecule on B-cell surfaces represent one of the

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most effective therapeutic approaches, as they cause B-cell depletion, which plays a key role in the autoimmune response underlying MS [6–8].

Ofatumumab (OFA) is a fully human monoclonal antibody self-administered at home via subcutaneous injection. It targets CD20 on B cells and was recently approved for relapsing multiple sclerosis (RMS) [8, 9]. The efficacy and safety of OFA were assessed in two identically designed randomized controlled trials, ASCLEPIOS I (NCT02792218) and ASCLEPIOS II (NCT02792231), which involved patients with RMS [10]. While these trials yielded promising results, real-world data on OFA remain limited [11, 12]. Therefore, bridging the gap between controlled studies and routine clinical practice is essential to fully characterize the therapeutic profile of OFA.

The primary objective of this study was to assess the efficacy and safety of OFA treatment in a real-world cohort of patients with relapsing MS over a 24-month period. Additionally, using a frailty index (FI)—a measure of increased susceptibility to adverse health outcomes due to multisystemic vulnerability [13]—we aimed to characterize the frailty status of patients with MS treated with OFA and to evaluate the predictive value of frailty for disability progression.

METHODS

Study Design

We collected clinical and magnetic resonance imaging (MRI) data from patients followed at 12 MS clinics in Central Italy. We evaluated the annualized relapse rate (ARR) in the 12 months before the start of OFA and 12 and 24 months after, the proportion of patients who experienced relapses, and any radiological activity during treatment with OFA at 12 and 24 months post-therapy initiation. The safety profile of OFA was also assessed. Clinical and MRI data were prospectively collected by each MS center during routine clinic visits, following national treatment guidelines [14], and retrospectively reviewed for this study.

Study Population, Clinical and Radiological Assessment

We enrolled patients with a diagnosis of RMS based on the 2017 McDonald criteria [15] who initiated treatment with OFA between April 2022 and January 2024. Eligibility required a minimum of 6 months of OFA therapy. Treatment was administered in accordance with European and Italian Medicines Agency guidelines. OFA was given as 20-mg subcutaneous injections at weeks 0, 1, and 2, followed by monthly 20-mg injections starting at week 4. Both treatment-naïve patients and those previously treated with moderate- or high-efficacy DMTs were included. Data on prior DMT use, most recent DMT before OFA, and washout durations were collected.

Disability was assessed by a neurostatus-certified MS specialist at baseline and at 12 and 24 months after starting OFA using the standard Expanded Disability Status Scale (EDSS) scoring system described by Kurtzke [16], which ranges from 0 (normal neurological examination) to 10 (death due to MS). This scale is based on the evaluation of eight functional systems (FS): pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (or mental), and other. Each FS is scored individually and then integrated with the assessment of ambulation capacity to assign a final EDSS score. All examinations were performed following standardized procedures and scored according to the Neurostatus e-scoring system to ensure inter-rater consistency.

We also assessed confirmed disability progression (CDP) at 24 months (CDP_24M), defined according to standard clinical criteria based on the EDSS: an increase of ≥ 1.5 points for patients with a baseline EDSS of 0, ≥ 1 point for those with baseline EDSS between 1.0 and 5.0, and ≥ 0.5 points for baseline EDSS ≥ 5.5.

Brain and spinal cord MRI scans were performed using 1.5 T or 3 T scanners, depending on the MS center. Standardized protocols included axial T1-weighted, T2-weighted, FLAIR, and gadolinium-enhanced T1 sequences. Radiological activity was defined as the presence of new or enlarging T2 lesions and/or contrast-enhancing T1 lesions at 12 and 24 months.

Whenever possible, the same scanner and acquisition protocol were used at each follow-up (FU).

The safety profile of OFA was evaluated by recording all adverse events (AEs) and severe adverse events (SAEs), classified according to the European Medicines Agency guidelines. AEs were defined as any medical occurrence in a subject administered a pharmaceutical product, regardless of a causal relationship with the treatment. SAEs were defined as AEs that resulted in death, were life-threatening, required hospitalization, or caused significant disability or incapacity, and were reported to the local pharmacovigilance system when applicable.

AEs were reported spontaneously by patients or identified during scheduled FU visits. They were monitored at each scheduled visit through structured clinical interviews, physical examination, and review of laboratory tests (e.g., complete blood count, liver and kidney function, and urinalysis). Investigators used a standardized safety checklist covering common and expected reactions (e.g., injection-site reactions, flu-like symptoms, infections), and all AEs were classified based on severity, duration, and potential causal relationship with OFA. Adverse events causality was assessed by the treating neurologist based on temporal relationship and biological plausibility.

Written informed consent was obtained from all study participants. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and it was approved by the local Ethics Committee of the University Hospital Policlinico Umberto I (No. 6357) on June 9, 2021.

Frailty

Frailty was measured using the deficit accumulation model, which suggests that frailty increases proportionally with the accumulation of age-related health deficits [17]. A Frailty Index (FI) was calculated following standard procedures [18, 19], considering clinical symptoms, signs, comorbidities, laboratory abnormalities, and disabilities unrelated to MS [20]. This model assumes that frailty increases with the number of health-related deficits an individual accumulates over time [18]. The FI was expressed as a continuous score between 0 and 1.

A Frailty Index (FI) was calculated for each patient by dividing the number of health deficits present by the total number considered. In this study, we used a 42-item FI, previously validated in the MS population [20]. The items included a combination of clinical symptoms and signs (e.g., fatigue, dizziness, pain, weight loss, falls), functional impairments (e.g., walking, dressing, feeding), comorbidities (e.g., hypertension, diabetes, depression, osteoarthritis), laboratory abnormalities (when available), non-MS-related disabilities. Each item was coded as 0 = deficit absent and 1 = deficit present. The final FI score ranges from 0 (no deficits) to 1 (all deficits present) and is calculated as the sum of the scores obtained across all items divided by 42, which is the total number of items included. Following literature-based thresholds, patients were categorized into relatively fit: $FI \leq 0.10$, least fit: $0.10 < FI \leq 0.21$, and frail: $FI > 0.2$. All investigators received specific training on the use of the frailty index in MS, and data were collected following a standardized form to ensure uniformity across centers.

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 (IBM, New York, USA). Descriptive statistics were calculated for demographic and clinical characteristics. The Shapiro–Wilk test was used to verify normal distribution of continuous variables. Parametric or non-parametric tests were applied accordingly. Parametric tests included the Student's *t* test and ANOVA. Non-parametric tests included the Mann–Whitney *U* test and Kruskal–Wallis test. Spearman's correlations were used to assess associations between the patients with FI and MS demographic and clinical features. Group comparisons were performed using chi-square tests, ANOVA, or the median test, as appropriate. Binary logistic regression and multivariate linear regression models were constructed to assess predictors of treatment-naïve status, relapse number, and disability progression. ROC curves and AUC values

were calculated to assess model performance. *P* values < 0.05 were considered significant.

RESULTS

A total cohort of 242 patients with MS (67.3% female and 32.7% male; mean age: 38.9 ± 10.3 years; disease duration: 7.7 ± 7.6 years) was enrolled in the study. Demographic and clinical characteristics of the whole cohort at baseline are shown in Table 1. A total of 95 patients (39.2%) were treatment-naïve, while 147 were switchers. Among switchers, 77 patients had used one DMT before starting OFA, while 70 patients had used two or more DMTs. A total of 89 (60.5%) patients changed treatment for efficacy, 43 (29.2%) for safety, 12 (8.3%) for tolerability and 3 (2%) for other reasons. The median washout period before switching to OFA was 4 weeks [interquartile range (IQR) = 2–15]. The mean FU duration was 15.4 ± 5.4 months, and the median was 12 months (IQR: 12–24 months). All patients completed the 12-month FU, while 103 completed the 24-month FU.

Table 1 Demographic and baseline clinical characteristics of the patients with RMS (*n* = 242) treated with OFA in a real-world setting

Characteristics	
Age, years, mean ± SD	38.9 ± 10.3
Females, *n* (%)	163 (66.8)
Male, *n* (%)	79 (32.7)
Disease duration, years, mean ± SD	7.7 ± 7.6
Treatment-naïve, *n*n (%)	95 (40)
First switchers, *n* (%)	77 (52.4)
EDSS at baseline, median (IQR)	2 (1–3)

Data are expressed as mean ± SD or median and IQR

EDSS Expanded Disability Status Scale, *IQR* interquartile range, *OFA* Ofatumumab, *RMS* relapsing multiple sclerosis, *SD* standard deviation

OFA Efficacy and Safety

The ARR reduced from 0.9, mean value in the 12 months before starting OFA, to 0.02, mean value after 24 months of treatment with OFA ($p < 0.001$). During the available FU, only four patients clinically relapsed (1.6%; 2 from fingolimod, 1 from natalizumab, and 1 from dimethylfumarate). The washout period for patients with clinical relapses was 5 weeks for those on fingolimod, 4 for those on natalizumab, and 2 weeks for those on dimethylfumarate. The reason for changing therapy were efficacy (1 patient from fingolimod and 1 from dimethylfumarate), safety (1 patient from natalizumab), and desire of pregnancy (1 patient from fingolimod). All relapses occurred during the first 6 months of therapy, with a mean time to first relapse of 3.0 ± 1.8 months after starting OFA treatment.

The EDSS total score did not change significantly during the FU [median at baseline: 2.0 (IQR = 1–3); at 12 months: 1.5 (IQR = 1–2.5); and at 24 months: 1.5 (IQR = 1–2.5); $p > 0.05$]. These data are shown in Fig. 1.

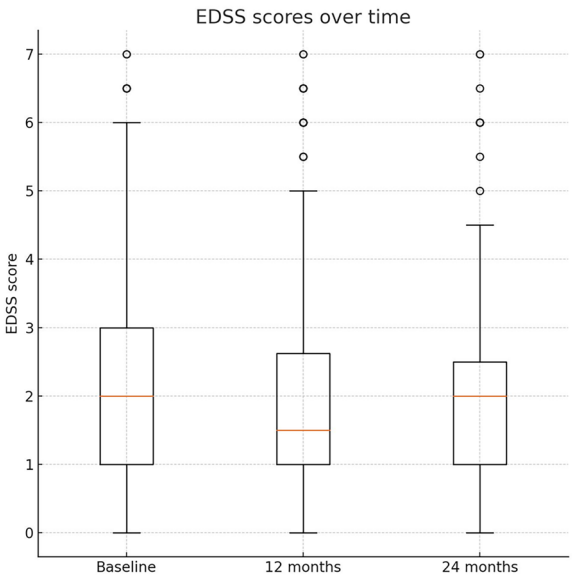

Fig. 1 EDSS before starting OFA and 12 and 24 months after. Data are expressed as median and interquartile range (IQR). *EDSS* Expanded Disability Status Scale, *OFA* ofatumumab

A total of 103 patients who completed a 24-month FU, 19 patients (18.4%) exhibited CDP. Among these 19 patients, 10 (53%) were switchers (6 from natalizumab, 1 from fingolimod, 1 from cladribine, and 2 from dimethyl fumarate), and 9 (47%) were treatment-naïve.

MRI activity was observed in 10 patients (4.1%) within the first 6 months of treatment and in 3 patients (1.2%) at the 12-month FU. No MRI activity was observed at 24 months. Of the 10 patients with radiological activity at 6 months, 2 were treatment-naïve and 8 were switchers (2 from natalizumab, 3 from fingolimod, 2 from dimethyl fumarate, 1 from glatiramer acetate). All had new T2 lesions, and 4 (one naïve and 3 switchers) also had gadolinium-enhancing T1 lesions. At 12 months, the 3 patients with MRI activity (only new T2 lesions) were all switchers: 1 from dimethyl fumarate (2-week washout), 1 from fingolimod (4-week washout), and 1 from natalizumab (4-week washout). Two of these patients who switched from natalizumab and from dimethylfumarate had also shown activity at 6 months.

The reported adverse events were flu-like syndrome during the first administration (83 patients, 34.3%), injection site reactions (20 patients, 8.2%) and infection (45 patients, 18.5%) of which 21 (46.6%) involved the upper respiratory tract and 24 (53.4%) the urinary tract. These results are summarized in Table 2. Only five patients discontinued OFA—three due to tolerability issues, one due to worsening of pre-existing autoimmune thrombocytopenia, and one due to pregnancy that was carried to term without complications. The new-born did not present any alterations at birth (length: 50 cm; weight: 2790 g; Apgar index at 1st min: 9; Apgar index at 5th min: 10).

Frailty and OFA

Frailty was measured in 239 of the 242 patients with MS enrolled. The 42-item FI used in the study exhibited a characteristic right-skewed distribution, with scores ranging from 0 to 0.48, and a median value of 0.02 (IQR = 0–0.09). Of the 239 patients with MS assessed for frailty, 187 were relatively fit (FI ≤ 0.10), 30 were least fit (0.10 < FI ≤ 0.21), and 22 patients were frail (FI > 0.21). A comparison of clinical and demographic characteristics according to frailty degree is summarized in Table 3. The three groups differed significantly in terms of age ($p < 0.001$), sex ($p = 0.04$), treatment-naïve status ($p = 0.002$), and EDSS score before starting OFA ($p < 0.001$), and at both 12 and 24 months after treatment initiation (all $p < 0.001$).

Frailty was positively correlated with age ($p = 0.001$) and EDSS ($p < 0.001$) and negatively correlated with treatment-naïve status ($p = 0.001$). A binary logistic regression model showed a significant negative association between FI and the likelihood of being treatment-naïve, independent of age, sex, EDSS before starting OFA, and disease duration [odds ratio (OR) 0.007; 95% confidence interval (CI) 0.001–0.393; $p = 0.015$]. However, no association was found between FI and the number of relapses during OFA treatment, independent of age, sex, disease duration, and EDSS ($p = 0.9$).

In the multivariate logistic regression analysis, the FI was significantly associated with 24-month disability progression (OR 1.05×10^{50}, 95% CI 6.26×10^{13}–1.78×10^{86}, $p = 0.0068$). Male sex was also independently associated with an increased risk of progression (OR = 5.25, 95% CI 1.09–25.4, $p = 0.039$). Age showed a non-significant trend toward higher risk (OR = 1.08, 95% CI: 0.99–1.17, $p = 0.081$), whereas disease duration, treatment-naïve status, and baseline EDSS were not significant predictors. The

Table 2 Summary of reported adverse events in the ofatumumab-treated cohort

Adverse event	*n* (%)	Severity
Flu-like syndrome	83 (34.3%)	Mild
Injection site reactions	20 (8.2%)	Mild
Infections	45 (18.5%)	Mild
Upper respiratory tract	21 (46.6% of infections)	Mild
Urinary tract	24 (53.4% of infections)	Mild

Data are presented as absolute numbers and percentages. All events were classified as mild. Infections are further broken down by site (upper respiratory and urinary tract)

Table 3 Characteristics of patients with MS according to their frailty levels

	Overall	Relatively fit (FI ⩽0.10)	Least fit (0.10 < FI ⩽ 0.21)	Frail (FI > 0.21)	*p*
Participants, *n*	239	187	30	22	
Age (years) mean ± SD	38.8 ± 10.4	37.4 ± 10.1	40.7 ± 10.4	48.1 ± 7.4	< 0.001[a]
Sex, *n* (%)					0.04[b]
Women	163 (68.2)	122 (65.2%)	21 (70%)	20 (90.9%)	
Men	76 (31.8)	65 (34.8%)	9 (30%)	2 (9.1%)	
MS duration, years, mean ± SD	10.9 ± 6.0	10.6 ± 11.7	8.3 ± 7.4	16.5 ± 9.3	0.02[a]
Treatment-naïve, *n*	94	84	4	6	0.002[a]
Previous DMTs before starting OFA, *n*					0.01[b]
1	68	53	9	6	
2	46	30	11	5	
≥ 3	31	20	6	5	
EDSS median before starting OFA, IQR	2 (1–3)	1.5 (1–2.5)	3 (2–4.5)	5.5 (4–6)	< 0.001[c]
EDSS median at 12 months after OFA, IQR	1.5 (1–2)	1.5 (1–2)	2.5 (2–3)	5 (3–6)	0.001[c]
EDSS median at 24 months after OFA, IQR	2 (1–2.5)	1.5 (1–2)	2.5 (2–5.5)	6 (4.5–6)	0.007[c]
Patients with relapse during OFA, *n*	4	3	0	1	0.6[a]

Data are expressed as mean ± SD, percentage or median and IQR. P-values refer to comparisons among the three frailty groups (relatively fit, least fit, frail)

DMTs disease-modifying treatments, *EDSS* expanded disability status scale, *FI* frailty index, *IQR* interquartile range, *MS* multiple sclerosis, *OFA* ofatumumab, *SD* standard deviation

[a]one-way ANOVA

[b]chi-square test

[c] Mann–Whitney *U* test

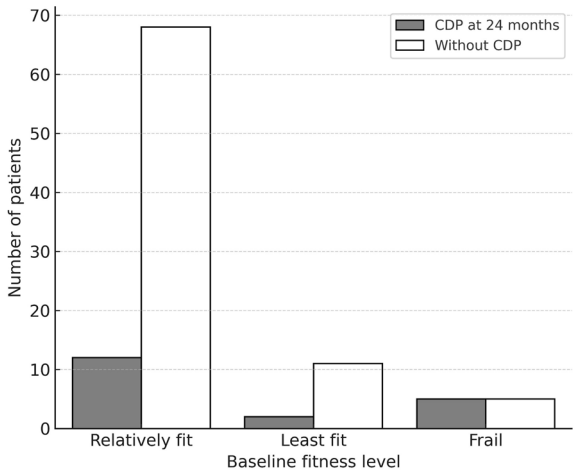

Fig. 2 Distribution of patients with and without confirmed disability progression at 24 months by baseline fragility level in an ofatumumab-treated cohort. The absolute number of patients with and without confirmed disability progression (CDP) at 24 months, stratified by baseline fragility level. Patients were categorized as relatively fit (n = 80), least fit (n = 13), or frail (n = 10) based on frailty assessment at treatment initiation. The proportion of patients with CDP increased with worsening baseline fitness, with the frail group showing the highest percentage (50%) compared to the relatively fit (15%) and the least fit (15.4%). Frailty categories are derived from a continuous frailty index ranging from 0 (no frailty) to 1 (severe frailty)

predictive model demonstrated good discriminative performance, with an area under the ROC curve (AUC) of 0.84. Moreover, when we stratified patients with MS according to baseline fragility level, among patients categorized as relatively fit (n = 80), 12 (15.0%) experienced CDP. In the least fit group (n = 13), CDP occurred in 2 patients (15.4%). Notably, the highest rate was observed in the frail subgroup (n = 10), with 5 patients (50.0%) reaching CDP within 24 months. The distribution of CDP events across fragility levels is illustrated in Fig. 2.

DISCUSSION

Our study provides real-world evidence supporting the effectiveness of OFA in controlling disease activity, both clinically and radiologically, as well as in determining the stability of disability measured with EDSS in patients with RMS during the 24-month FU period. Additionally, OFA appears to be a safe and well-tolerated treatment for MS. Our study also highlights the potential role of frailty as a predictor of long-term disability progression, reinforcing the importance of personalized treatment strategies in MS care and the need of active monitoring and treatment of comorbidities.

Several precautions were taken to minimize the influence of confounding factors. To reduce inter-rater variability in frailty assessment, all examiners were thoroughly trained in administering the FI. Clinical assessments were conducted by neurostatus-certified MS specialists, and radiological assessments were performed by neuroradiologists with expertise in MS.

To our knowledge, this is the first study to investigate the long-term efficacy and safety of OFA in a large cohort of patients with MS in a real-world setting. Consistent with previous controlled trials (ASCLEPIOS I/II and ALITHIOS) [10, 21], we confirmed the low relapse rate with OFA and the near-complete reduction in MRI lesions. Notably, the only four relapses occurred during FU, all within the first 6 months of therapy and in patients switching from other DMTs. This may reflect transient disease reactivation due to prior therapies and short washout periods. No new relapses occurred beyond the six-month mark, which may suggest that OFA has the potential to exert a rapid and sustained anti-inflammatory effect in real-world settings. Our findings also align with two recent real-word cohort studies with shorter FU [11, 12]. In these studies, however, patients were older and disease duration longer than our cohort thus suggesting in a real word setting an early use of HET in our MS centers. Our study suggested the high efficacy of OFA even up to 24 months FU in real-world settings.

MRI findings support this interpretation. Most patients remained free from radiological activity at both 12- and 24-month FU assessments. Importantly, patients with MRI activity were predominantly switchers, and some had already shown radiological activity during the

early phase of OFA treatment. These data align with the known effectiveness of OFA in reducing inflammatory activity and confirm its real-world applicability.

Furthermore, we observed a low risk of disability progression, suggesting that OFA may exert a rapid effect in controlling disability progression from the early months of therapy. These findings are in line with data from controlled clinical trials [21]. Recent studies have also shown that OFA is comparable in efficacy to other highly efficacious monoclonal antibody therapies (i.e., alemtuzumab, natalizumab, and ocrelizumab) and ranks among the most effective DMTs in reducing ARR in patients with RMS [7, 22, 23].

In line with literature indications that early initiation of high-efficacy treatment in RMS leads to better long-term outcomes compared with delayed initiation, in our real-world cohort about 40% of patients were treatment naïve and 53% of switchers were undergoing their first DMT switch.

Regarding safety, OFA administration was associated with a higher incidence of post-administration reactions, such as flu-like symptoms, especially after the initial dose. However, these events subsided in the short term. This is consistent with data from regulatory trials and recently reported real-world data [11].

In our study, only five patients discontinued OFA, three due to tolerability issues, one due to worsening of pre-existing autoimmune thrombocytopenia, and one due to pregnancy that was carried to term without complications. The newborn did not present any alterations at birth. Thus, OFA can be considered a well-tolerated drug.

In this study, we first confirmed that frailty due to non-MS related clinical burden correlates with age and EDSS score in MS [20]. Additionally, we found that frailty is associated with patients who have started OFA due to previous DMT failure. This novel finding supports the hypothesis that individual frailty associated with non-MS related clinical burden may play a role in MS progression.

The lack of correlation observed between frailty index and relapses during OFA treatment may be attributed to the short-term FU, and the high efficacy of OFA in reducing inflammation compared to moderately effective DMT. Notably, only four patients experienced relapses during OFA treatment during the observation period and three of them had discontinued drugs interfering with lymphocyte trafficking. Moreover, the low number of patients who experienced a clinical relapse during OFA treatment limiting the statistical power to detect associations with FI.

An interesting finding emerging from our study was that a higher numerical frailty score at baseline was a strong independent predictor of 24-month confirmed disability progression, even after adjusting for age, sex, disease duration, treatment-naïve status, and baseline EDSS. This association highlights the clinical relevance of incorporating frailty assessment into the management of patients with RMS. In our cohort treated with OFA, patients classified as frail had a markedly higher rate of CDP compared to those classified as relatively fit and least fit. This gradient suggests that frailty may capture elements of physiological vulnerability not fully addressed by traditional disability scales such as the EDSS.

These findings are in line with emerging evidence that frailty—originally developed in geriatric medicine—has prognostic value in chronic neurological diseases, including MS. The increased risk of progression among frail individuals may reflect reduced functional reserve, multimorbidity, or subclinical burden of disease, potentially affecting both neurodegenerative and repair mechanisms.

In addition, this association persisted despite uniform treatment exposure, suggesting that baseline frailty might independently influence long-term clinical outcomes, even under high-efficacy therapy. This supports the integration of frailty assessment tools into routine clinical evaluation, both for prognostic stratification and for tailoring FU strategies and therapeutic expectations.

Importantly, while a high baseline frailty score predicted 24-month disability progression, this does not undermine the value of initiating or continuing DMTs in frail patients. On the contrary, these individuals should be considered for tailored therapeutic strategies that combine high-efficacy MS treatments with close

monitoring and management of comorbidities. Frailty assessment may thus serve as a useful tool to personalize treatment approaches, rather than to exclude patients from receiving DMTs. Frailty likely reflects a broader systemic vulnerability that may interact with neurodegenerative mechanisms underlying long-term disability accrual in MS.

From a pathophysiological perspective, emerging evidence indicates that the pathophysiology of MS involves a complex interplay between inflammation and neurodegeneration from the earliest stages of the disease [24, 25]. In this context, frailty might exacerbate or contribute biological processes that promote neurodegeneration—such as chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, loss of proteostasis, and impaired repair mechanisms—which are thought to underlie disease progression in MS [26]. This further emphasizes the prognostic utility of frailty in MS and suggests that non-MS-related health deficits can influence long-term outcomes, even in patients receiving high-efficacy therapies. Early identification of frail patients could enable more tailored interventions, including intensified monitoring and multidisciplinary care approaches.

Our study has several limitations. Its retrospective design may have introduced selection and information biases. Follow-up duration and imaging protocols varied slightly across centers, and long-term outcomes beyond 24 months were not available. MRI scanner heterogeneity and protocol variability are relevant limitations in real-world imaging studies. Whenever feasible, FU imaging was performed using the same scanner and protocol as the baseline exam, but some variability across centers was present, reflecting real-world clinical practice. Despite these limitations, the study's multicenter nature and large sample size enhance the generalizability of our findings.

CONCLUSION

Our findings of sustained reductions in relapse rates, MRI lesion activity, and disability progression risk with OFA treatment may contribute to growing evidence supporting the early initiation of high-efficacy therapies in RMS. Importantly, our data also suggested a rapid control of disease activity and progression from the first year of treatment and up to 24 months in real-world settings, contributing to the growing evidence supporting the early-initiation OFA. These results also highlight the favorable benefit–risk profile of OFA treatment for patients with RMS. Access to highly efficacious treatments like OFA can help reduce the disease burden, slow RMS progression, and contribute to long-term improvements in quality of life. Importantly, our results highlight that baseline frailty—reflecting cumulative health deficits unrelated to MS—is a significant predictor of disability progression. These findings underscore the need to assess frailty at treatment initiation and actively treat comorbidities. Further prospective, long-term studies are warranted to validate the role of frailty in MS prognosis and to optimize individualized treatment strategies.

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Data Availability. The datasets generated during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest. Gina Ferrazzano, Roberta Fantozzi, Shalom Haggiag, Doriana Landi, Francesca Napoli, Maria Chiara Buscarinu, Leonardo Malimpensa, Assunta Bianco, Giovanna Borriello, Elena Barbuti, Fabiana Marinelli, Fabrizia Monteleone, Francesca Marchione, Nicola Falcone, Marta Altieri, Giorgio Leodori, Daniele Belvisi, Fabio Buttari, Valeria Pozzilli, Alessandra Cicia, Antonio Cortese, Francesco Sica, Anna Chiara Landi, Elisabetta Ferraro, Carlo Pozzilli, Massimiliano Mirabella, Carla Tortorella, Girolama Alessandra Marfia, Diego Centonze, Marco Salvetti and Antonella Conte declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the local Ethics Committee of the University Hospital Policlinico Umberto I (No. 6357) on June 9, 2021. Informed consent was obtained from all individual participants included in the study.

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