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ORIGINAL RESEARCH ARTICLE

Real-World Effectiveness and Safety of Ofatumumab in Relapsing Multiple Sclerosis: Comparison of Treatment-Naïve Patients and Switchers in a Multicenter Cohort

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Abstract

Background Ofatumumab (OFA) is a fully human anti-CD20 monoclonal antibody approved for the treatment of relapsing multiple sclerosis (RMS). Real-world data on its effectiveness and safety remain limited.

Objective To assess the effectiveness and safety of OFA in a large Italian RMS cohort and to examine the impact of prior treatment exposure on clinical, radiological, and safety outcomes in routine clinical practice.

Methods This retrospective, multicenter study included adults with RMS who initiated OFA and had at least one follow-up visit. Patients were classified as treatment-naïve, switching from moderate-efficacy therapies (MET), or switching from high-efficacy therapies (HET). Outcomes included annualized relapse rate (ARR), magnetic resonance imaging (MRI) activity, disability measures (including confirmed disability worsening and improvement), no evidence of disease activity (NEDA-3), and adverse events (AEs).

Results A total of 424 patients were analyzed, with a mean follow-up of 1.32 (± 0.61) years: 101 (23.8%) treatment-naïve and 323 (76.2%) switchers, of whom 113 were previously treated with MET and 210 with HET. During treatment, ARR decreased significantly from 0.486 to 0.027 (94.5% reduction; $p < 0.001$), with comparable relative reduction observed across all subgroups. MRI activity was significantly diminished, and at 12 months, 79.3% of evaluable patients achieved NEDA-3, with no significant differences between naïve, MET, and HET subgroups. Overall, OFA was well tolerated, with predominantly mild injection-related reactions and low discontinuation rates, mainly related to pregnancy planning with favorable outcomes. Infections were the only safety outcome that differed significantly among groups, occurring in 0.9% of naïve patients, 1.7% of MET switchers, and 9.5% of HET switchers ($p = 0.001$). Prior exposure to HET was the only independent predictor of infections.

Conclusions These findings support OFA as an effective and generally safe option for RMS across various treatment sequences, while suggesting enhanced infection monitoring in patients switching from HETs.

1 Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system (CNS) characterized by multifocal inflammatory demyelination, axonal injury, and widespread neurodegeneration. It represents a leading cause of long-term neurological disability among young adults [1–3]. Neuropathological studies have demonstrated the coexistence of acute inflammatory lesions, slowly expanding demyelinating plaques, compartmentalized meningeal inflammation, and sustained microglial activation, all of which contribute to the progressive course of the disease [2–4].

Over the past decade, converging immunological and molecular evidence has elucidated the pivotal role of B cells in MS pathogenesis. B cells act not only as precursors to antibody-producing cells but also as effective antigen-presenting cells and significant producers of pro-inflammatory cytokines that facilitate aberrant T-cell activation and CNS infiltration [5, 6]. The clonal relationships observed among B-cell populations in the blood, cerebrospinal fluid, and CNS tissue highlight a recirculating B-cell axis that contributes to both acute inflammatory responses and chronic, smoldering

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Key Points

Ofatumumab achieved substantial reductions in relapse rate and MRI activity, with high rates of NEDA-3, across treatment-naïve patients and switchers from both moderate- and high-efficacy therapies in a large Italian real-world cohort.

Disability outcomes remained stable over follow-up, with no meaningful differences across treatment subgroups, as confirmed by multivariable sensitivity analyses adjusting for baseline disease characteristics.

Prior exposure to high-efficacy therapies was the only independent predictor of infection risk under ofatumumab, likely reflecting long-lasting immunomodulatory effects of previous treatments rather than a direct pharmacological effect of ofatumumab itself.

inflammation [4, 7]. These findings provide a robust biological rationale for the selective targeting of CD20-expressing B cells in MS [5–8].

Anti-CD20 monoclonal antibodies have demonstrated significant efficacy in the treatment of relapsing MS (RMS), evidenced by rapid suppression of new focal inflammatory activity, substantial reductions in gadolinium-enhancing lesions and new/enlarging T2 lesions, and a decreased risk of relapse-associated disability worsening [9, 10]. Ofatumumab (OFA), a fully human anti-CD20 monoclonal antibody formulated for subcutaneous self-administration, achieves rapid and sustained peripheral B-cell depletion while maintaining stable pharmacokinetic and pharmacodynamic profiles [10, 11]. In the pivotal ASCLEPIOS trials, OFA demonstrated superiority over teriflunomide (TERI) across both clinical and magnetic resonance imaging (MRI) endpoints [12]. Furthermore, long-term extension data from the ALITHIOS study confirmed durable efficacy and a stable safety profile with continuous monthly dosing [13, 14].

While randomized controlled trials (RCTs) provide robust data on efficacy and safety data under standardized conditions, real-world evidence is essential to evaluate the performance of OFA in broader clinical settings, including patients with longer disease durations, comorbidities, or prior exposure to moderate-efficacy therapies (MET) and high-efficacy therapies (HET). Treatment sequencing is increasingly recognized as a critical factor influencing clinical outcomes in MS, with transitions between DMT classes potentially affecting both treatment response and susceptibility to infectious complications or rebound inflammatory activity [10, 11, 15–20]. Therefore, understanding how previous DMT exposure impacts the effectiveness and safety of OFA is crucial for optimizing therapeutic strategies.

To date, real-world evidence (RWE) on OFA remains limited to a few single-center or small multicenter cohorts, predominantly reporting short-term outcomes in selected populations [21–27]. Larger, multicenter studies examining the impact of prior treatment exposure on OFA effectiveness and safety are therefore needed.

This multicenter real-world study aimed to assess the effectiveness and safety of OFA in RMS across four Italian MS centers and to examine the impact of prior treatment on clinical, radiological, and safety outcomes in routine clinical practice.

2 Methods

This retrospective, multicenter, real-world study was conducted across four Italian tertiary MS referral centers located in Bari, Genoa, Turin, and Cagliari, collectively representing different geographic areas of the country. Clinical and magnetic resonance imaging (MRI) data were extracted from electronic medical records as part of routine clinical practice. Data quality was ensured through a standardized data extraction protocol applied uniformly across all participating centers. Checks for duplicate records, data completeness, and consistency of key variables were performed prior to analysis. The study received approval from local ethics committees, and all anonymized data was managed in accordance with institutional and international guidelines. Furthermore, this study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Adults aged 18 years or older with RMS diagnosed in accordance with the 2017 McDonald criteria [28], who initiated OFA treatment between March 2022 and March 2025 and had at least one clinical or radiological follow-up assessment were eligible for inclusion.

Patients were classified into three groups based on their treatment history:

1. Treatment-naïve.
2. Switchers from MET: interferon beta, glatiramer acetate, TERI, dimethyl fumarate, and azathioprine.
3. Switchers from HET: natalizumab (NTZ), ocrelizumab (OCRE), sphingosine-1-phosphate (S1P) receptor modulators, cladribine (CLAD), and alemtuzumab.

For each patient, data were collected on demographic and disease characteristics, prior exposure to DMTs, Expanded Disability Status Scale (EDSS) scores, relapse occurrences, MRI findings, adverse events (injection-related reactions,

infections, and neoplasms), and reasons for treatment discontinuation, including interruptions related to pregnancy. Radiological assessments, including the identification of new or enlarging T2-weighted lesions and gadolinium-enhancing (Gd+) T1-weighted lesions, were performed using 1.5T or 3T scanners in accordance with local protocols based on MAGNIMS criteria [29].

Clinical endpoints included annualized relapse rate (ARR), confirmed disability worsening (CDW) at 6 months, confirmed disability improvement (CDI) at 6 months, and no evidence of disease activity (NEDA-3). NEDA-3 status was evaluated in patients with complete 12-month follow-up data, including available MRI assessment at that timepoint. Patients who had not yet reached 12 months of follow-up at the time of data extraction, or for whom MRI data were unavailable at 12 months, were excluded from NEDA-3 analysis.

A relapse was defined as the occurrence of new or worsening neurological symptoms lasting at least 24 h, in the absence of fever or infection, with objective confirmation by a neurologist. Corticosteroid treatment was recorded but not required for relapse definition. CDW was defined as an increase in EDSS score of ≥ 1.5 points from a baseline score of 0, ≥ 1.0 point from a baseline score of 1.0–5.5, or ≥ 0.5 points from a baseline score of ≥ 6.0, sustained for at least 6 months. CDI was defined as a decrease in EDSS score of ≥ 1.5 points from a baseline score of 1.5, ≥ 1.0 point from a baseline score of 2.0–6.0, or ≥ 0.5 points from a baseline score of ≥ 6.5, sustained for at least 6 months, in the absence of a relapse in the preceding 30 days. These definitions are consistent with those used in pivotal MS clinical trials and current real-world observational studies.

For inclusion in effectiveness analyses, a minimum follow-up duration of 6 months was required for CDW and CDI. ARR and NEDA-3 analyses required a minimum follow-up of 12 months, given the time-dependent nature of these outcomes.

2.1 Statistical Analysis

ARR prior to and during OFA treatment was estimated using negative binomial regression, adjusted for age, sex, baseline EDSS, and relapse history. MRI changes were evaluated using McNemar's test alongside corresponding risk ratios. Time-to-event outcomes (CDW, CDI) were assessed through Kaplan–Meier survival curves and Cox proportional hazards models. The risk of infections was assessed using multivariable logistic regression. Between-group comparisons for categorical variables were performed using chi-squared or Fisher's exact tests, as appropriate. Continuous variables were compared using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test on the basis of distributional assumptions. To assess the robustness of subgroup comparisons against baseline heterogeneity, sensitivity analyses were performed for all key outcomes other than ARR: logistic regression for NEDA-3; Cox proportional hazards models adjusted for age, sex, baseline EDSS, disease duration, prior relapse history, and baseline MRI activity for CDW and CDI; and Firth's penalized logistic regression for MRI outcomes given the relatively low event rates. Statistical significance was set at $p < 0.05$. All analyses were performed using R software (version 4.5.0).

3 Results

A total of 424 patients with RMS were included in the study. The mean age at OFA initiation was 39.1 ± 10.8 years, with 215 patients (50.7%) being female. The mean disease duration was 10.3 ± 8.8 years. At baseline, the median EDSS score was 2.5 [interquartile range (IQR) 1.5–3.5]. The mean time since diagnosis to OFA was 7.6 ± 9.3 years. The mean follow-up period under OFA was 1.32 ± 0.61 years. OFA was administered as the first DMT in 101 patients (23.8%; naïve group), whereas 323 patients (76.2%) switched from at least one prior therapy. Among switchers, 113 (35.0%) had previously received MET and 210 (65.0%) had received HET. At baseline, patients experienced an average of 2.19 ± 2.12 relapses. In the 12 months preceding OFA initiation, the mean relapse rate was 0.51 ± 0.53.

Baseline MRI data revealed Gd+ T1 lesions in 24.1% (102/424) and new/enlarging T2 lesions in 52.6% (223/424) of evaluable patients. MRI activity was more frequent in naïve patients than in those previously treated: Gd+ T1 lesions were observed in 49.5% of naïve patients versus 17.3% of switchers, while new/enlarging T2 lesions were identified in 62.4% of naïve patients versus 49.4% of switchers. Further stratification of switchers indicated that Gd+ lesions were present in 23.9% of MET patients and 11.9% of HET patients, with new/enlarging T2 lesions detected in 76.1% and 35.2%, respectively (Table 1).

The adjusted ARR decreased from 0.486 (95% CI 0.449–0.527) during the pre-treatment period to 0.027 (95% CI 0.016–0.039) under OFA treatment, representing a 94.5% relative reduction ($p < 0.001$). The magnitude of ARR reduction was consistent across the three groups. Specifically, in treatment-naïve patients, the ARR declined from 0.792 (95% CI 0.721–0.869) to 0.032 (95% CI 0.009–0.057); in MET switchers, from 0.529 (95% CI 0.437–0.616) to 0.025 (95% CI 0.000–0.049); and in HET

switchers, from 0.346 (95% CI 0.290–0.417) to 0.022 (95% CI 0.000–0.038). Comparisons of rate ratios revealed no significant differences among the subgroups (Table 2).

Following OFA initiation, MRI activity significantly decreased across all treatment groups. The proportion of patients exhibiting Gd+ T1 lesions declined from 24.1% at baseline to 2.1% (9/424), representing an absolute reduction of 21.9 percentage points (95% CI 17.6–26.2) and a relative reduction of 91.2% (95% CI 82.8–95.5; $p < 0.001$). Among treatment-naïve patients, this proportion decreased from 49.5 to 2.0%, corresponding to a 96.0% relative reduction. In MET and HET switchers, the proportion declined from 23.9 to 1.8% (92.6% relative reduction) and from 11.9 to 2.4% (80.0% relative reduction), respectively, with overlapping confidence intervals (Table 3).

The proportion of new or enlarging T2 lesions decreased from 52.6 to 12.7%, representing an absolute reduction of 39.9 percentage points (95% CI 34.1–45.6) and a relative reduction of 75.8% (95% CI 68.4–81.4; $p < 0.001$). These reductions were observed consistently across subgroups: from 62.4 to 16.8% in treatment-naïve patients (73.0% relative reduction), from 76.1 to 12.4% in MET switchers (83.7% relative reduction), and from 35.2 to 11.0% in HET switchers (68.9% relative reduction) (Table 4).

At 24 months, the Kaplan–Meier estimate for CDW was 13.2%, based on 19 events among 424 patients. No significant differences were observed among the treatment-naïve subgroup (10.7%), the MET subgroup (13.8%), and the HET subgroup (5.7%). The hazard ratios comparing HET versus naïve and MET versus naïve were 0.55 (95% CI 0.20–1.53) and 0.75 (95% CI 0.25–2.23), respectively. CDI occurred in 15 patients (9.5%), with rates of 9.1% in treatment-naïve patients, 2.9% in MET switchers, and 6.3% in HET switchers; these differences were not statistically significant (Table 5).

Among the 237 patients with complete 12-month follow-up data, 79.3% achieved NEDA-3 status. The rates were similar across groups: 76.8% in treatment-naïve patients, 81.5% in MET patients, and 79.3% in HET patients. The loss of NEDA-3 status was primarily attributable to CDW (12.2%) or new T2 lesions (7.1%), whereas relapses (4.2%) and Gd+ lesions (1.2%) were infrequent.

After adjustment for age, sex, baseline EDSS, disease duration, prior relapse history, and baseline MRI activity, no statistically significant differences between treatment groups were observed for NEDA-3, CDW, CDI, or MRI outcomes. These results confirm the consistency of treatment effects across subgroups independent of baseline disease characteristics. Detailed results of the sensitivity analyses are provided in Supplementary Table S1a and b.

Safety data were available for all 424 patients included in the study. Overall, 17.8% of patients experienced at least one adverse event during OFA therapy. The frequency of injection reactions, observed in 12.5% of the cohort, was similar across the treatment-naïve, MET, and HET patient subgroups ($p = 0.454$). Three neoplasms (0.7%) were reported, including one colonic adenoma and two intraductal papillary mucinous neoplasms, with no significant differences between subgroups. Overall, 19 treatment discontinuations (4.5%) occurred during follow-up: 2 in treatment-naïve patients and 17 among switchers, with no statistically significant difference between groups (global $p = 0.93$). Of these discontinuations, seven were pregnancy related. Six pregnancies progressed to full term, resulting in healthy newborns without obstetric complications or congenital anomalies; one pregnancy was ongoing at the time of data

Table 1 Baseline demographic and clinical characteristics of the study population

Characteristic	Value
Age at OFA initiation, years (mean ± SD)	39.1 ± 10.8
Female sex, *n* (%)	215 (50.7)
Disease duration, years (mean ± SD)	10.3 ± 8.8
EDSS, median (IQR)	2.5 (1.5-3.5)
Time since diagnosis to OFA, years	7.6 ± 9.3
Follow-up under OFA, years (mean ± SD)	1.32 ± 0.61
Treatment-naïve, *n* (%)	101 (23.8)
Switchers, *n* (%)	323 (76.2)
From MET	113 (35.0)
From HET	210 (65.0)
Relapses in previous 12 months	0.51 ± 0.53
Baseline Gd+ T1 lesions, *n/N* (%)	102/424 (24.0)
Baseline new/enlarging T2 lesions, *n/N* (%)	223/424 (52.5)

OFA ofatumumab, *SD* standard deviation, *IQR* interquartile range, *EDSS* Expanded Disability Status Scale, *MET* moderate-efficacy therapy, *HET* high-efficacy therapy, *Gd+* gadolinium-enhancing, DMT disease-modifying therapy, *n* number of patients, *N* total evaluable patients

Table 2 Annualized relapse rate before and during OFA treatment, by treatment group

Group	ARR pre-OFA	ARR under OFA	Relative reduction (%)	Rate ratio
Overall	0.486	0.027	94.5	0.055
Naïve	0.792	0.032	95.9	0.041
MET	0.529	0.025	95.2	0.048
HET	0.346	0.022	93.7	0.063

ARR estimates derived from negative binomial regression adjusted for age, sex, baseline EDSS, and relapse history

ARR annualized relapse rate, *OFA* ofatumumab, *MET* moderate-efficacy therapy switchers, *HET* high-efficacy therapy switchers

Table 3 Proportion of patients with gadolinium-enhancing T1 lesions before and after OFA treatment, by treatment group

Group	Baseline (%)	Follow-up (%)	Absolute reduction (%)	Relative reduction (%)	Risk ratio
Overall	24.1	2.1	21.9	91.2	0.09
Naïve	49.5	2.0	47.5	96.0	0.04
MET	23.9	1.8	22.1	92.6	0.08
HET	11.9	2.4	9.5	80.0	0.20

Reductions assessed using McNemar's test with corresponding risk ratios

OFA ofatumumab, *Gd+* gadolinium-enhancing, *MET* moderate-efficacy therapy switchers, *HET* high-efficacy therapy switchers

Table 4 Proportion of patients with new or enlarging T2 lesions before and after OFA treatment, by treatment group

Group	Baseline (%)	Follow-up (%)	Absolute reduction (%)	Relative reduction (%)	Risk ratio
Overall	52.6	12.7	39.9	75.8	0.24
Naïve	62.4	16.8	45.6	73.0	0.27
MET	76.1	12.4	63.7	83.7	0.16
HET	35.2	11.0	24.2	68.9	0.31

Reductions assessed using McNemar's test with corresponding risk ratios

OFA ofatumumab, *MET* moderate-efficacy therapy switchers, *HET* high-efficacy therapy switchers

Table 5 Disability outcomes: confirmed disability worsening and improvement by treatment group

Outcome	Overall	Naïve	MET	HET
CDW events, *n*	19	7	7	5
CDW at 24 months (%)	13.2	10.7	13.8	5.7
CDI events, *n*	15	6	3	9
CDI at 24 months (%)	9.5	9.1	2.9	6.3

CDW and CDI assessed at 6-months with confirmation using Kaplan–Meier estimates at 24 months

CDW confirmed disability worsening, *CDI* confirmed disability improvement, *MET* moderate-efficacy therapy switchers, *HET* high-efficacy therapy switchers, *HR* hazard ratio, *CI* confidence interval

Table 6 Overall safety outcomes by treatment group

Safety parameter	Overall	Naïve	MET	HET
Any adverse event, *n* (%)	17.8	16.8	15.9	20.9
Injection-related reactions, *n* (%)	12.5	14.8	14.1	10.5
Neoplasms, *n* (%)	0.7	0.9	0	0.6
Treatment discontinuations, *n* (%)	4.5	2	6	11

Values expressed as percentages unless otherwise indicated

OFA ofatumumab, *MET* moderate-efficacy therapy switchers, *HET* high-efficacy therapy switchers

extraction. In all cases, OFA therapy was temporarily discontinued upon recognition of pregnancy and was successfully resumed postpartum on the basis of clinical judgment, with no subsequent safety concerns (Table 6).

Overall, 5.4% of patients developed at least one infection; however, infection rates varied significantly according to prior DMT exposure: 0.9% (1/101) among treatment-naïve patients, 1.7% (2/113) among MET switchers, and 9.5% (20/210) among HET switchers (global $p = 0.001$). Infectious complications were predominantly urinary tract infections and did not require hospitalization in any case. Pairwise comparisons confirmed a significantly higher risk of infection in HET switchers compared with both naïve patients (Bonferroni-corrected $p = 0.0096$) and MET switchers ($p = 0.0286$), whereas no significant difference was observed between naïve and MET groups.

Logistic regression analyses identified group classification (naïve, MET, HET) as the only significant predictor of infection risk (global $p = 0.0006$). In the multivariable model using HET switchers as the reference group, the adjusted odds of infection were significantly lower in naïve patients [odds ratio (OR) 0.10, 95% CI 0.013–0.73, $p = 0.023$] and in MET switchers (OR 0.18, 95% CI 0.041–0.78, $p = 0.022$).

4 Discussion

In this large Italian real-world cohort, OFA demonstrated a rapid and substantial suppression of inflammatory activity, evidenced by a greater than 90% reduction in ARR, a near-complete elimination of Gd+ lesions, and a 75% decrease in new or enlarging T2 lesions. Approximately 80% of patients achieved NEDA-3 status at 12 months, thereby corroborating in routine practice the high efficacy reported in the ASCLEPIOS trial and its long-term extension studies. The magnitude of benefit observed across all evaluated endpoints highlights the consistency and depth of disease control achievable through continuous subcutaneous B-cell depletion [12–14].

Furthermore, the large sample and multicenter nature of our cohort, one of the largest Italian real-world datasets on OFA, enhance the robustness and generalizability of these findings, extending the emerging body of RWE on OFA, which has thus far been limited to smaller cohorts with shorter follow-up or more restricted patient populations [21–26].

In this context, disability outcomes remained stable over follow-up, with low rates of confirmed disability worsening and no meaningful differences across treatment-naïve, MET, and HET subgroups. Disability progression contributed minimally to NEDA-3 loss, whereas residual focal inflammatory activity was the predominant driver. Together, these findings indicate that continuous subcutaneous CD20-mediated B-cell depletion with OFA supports early stabilization of disability trajectories in real-world RMS populations [17, 30–33] .

A notable finding of our study is the descriptively similar clinical and radiological benefit observed both in treatment-naïve patients and in those switching from MET or HET. Although direct inferential comparisons between subgroups are limited by baseline heterogeneity in disease activity, the convergence of outcomes across groups appears consistent and aligns with emerging RWE and supports the biological rationale for CD20-targeted therapies. The sustained therapeutic response observed in patients switching from HET underscores the biological robustness of OFA's mechanism of action, suggesting that effective B-cell depletion remains clinically impactful even in patients with prolonged disease duration and prior exposure to HET [21–23, 34, 35]. This consistency was further confirmed by sensitivity analyses adjusting for baseline disease activity and clinical covariates, which yielded no significant differences between treatment groups across any of the evaluated outcomes (Supplementary Tables S1a and b).

The safety profile of OFA aligns with previous evidence, characterized primarily by mild injection-related adverse events and the absence of new safety concerns [36]. One clinically significant finding was observed: patients switching from HET demonstrated a substantially higher rate of infections, independent of demographic or disease-related factors. Importantly, this association most likely reflects the cumulative immunological burden imposed by prior HET exposure rather than a direct effect of OFA itself. In accordance with current prescribing guidelines, all patients initiated OFA with lymphocyte B counts and immunoglobulin levels within normal ranges, excluding active immunosuppression at treatment onset as a contributing factor. Nevertheless, prior exposure to agents such as S1P receptor modulators, NTZ, OCRE, or CLAD may induce long-lasting immunomodulatory effects that are not fully captured by standard laboratory parameters at the time of OFA initiation, thereby contributing to a residual susceptibility to infections [18, 21, 37–39]. Notably, this association has not been previously documented in OFA real-world studies, providing clinically relevant insights for optimizing treatment sequencing and infection monitoring strategies.

Beyond infection risk, reproductive safety also warrants consideration in clinical practice. In our cohort, several pregnancies occurred during OFA treatment, all managed with prompt treatment discontinuation and without adverse obstetric or neonatal outcomes. Although OFA-specific evidence remains limited, current data on anti-CD20 agents, including recent real-world cohorts and case reports, suggest that early unintentional gestational exposure does not appear to confer major short-term risks, while emphasizing the need for neonatal B-cell monitoring and adjusted vaccination schedules [29, 40, 41].

Despite these findings, the following limitations should be acknowledged. The retrospective design and multicenter nature of data collection introduce inherent constraints, including the absence of uniformly recorded variables such as reasons for switching to OFA. As all participating centers are tertiary MS referral centers, the cohort may be enriched for patients with more severe disease profiles and greater prior treatment exposure, which may limit generalizability to broader clinical settings. Similarly, inclusion of patients with at least one post-baseline follow-up assessment may introduce a selection bias toward more favorable effectiveness and safety estimates. Baseline differences in disease activity across subgroups introduce potential confounding by indication; however, sensitivity analyses adjusting for key covariates confirmed the absence of significant inter-group differences across all evaluated outcomes. Of note, the mean follow-up of 1.32 years, while consistent with other early real-world studies on OFA, limits the assessment of long-term disability outcomes, and CDW and CDI rates should be interpreted accordingly. Regarding

MRI methodology, assessments were performed locally rather than by a centralized reader, and although each patient underwent baseline and follow-up scans on the same scanner using an identical protocol, inter-rater variability across sites cannot be fully excluded. Finally, the absence of serial immunoglobulin levels, lymphocyte subset monitoring, and standardized infection severity grading limits the mechanistic interpretation of the observed infection risk and precludes systematic comparison of infectious outcomes with other studies.

5 Conclusions

Taken together, the present findings suggest that OFA is associated with effective control of inflammatory disease activity in routine clinical practice, as reflected by substantial reductions in relapse rates and MRI activity, alongside high rates of NEDA-3 achievement and overall stability of disability measures over follow-up. The consistency of these clinical and radiological outcomes across treatment-naïve patients and those switching from MET or HET supports the reproducibility of treatment effects across different therapeutic sequences. With regard to safety, the tolerability profile observed in this cohort appears broadly consistent with that reported in clinical trials and previous real-world studies. Notably, the higher incidence of infections among patients switching from HET may reflect the cumulative impact of prior immunomodulatory exposure rather than a direct effect of OFA itself, underscoring the importance of treatment history when interpreting safety outcomes. Drawing on a large Italian multicenter real-world cohort of OFA treated patients, the present study extends available evidence and provides clinically relevant insights for treatment sequencing in routine practice.

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Declarations

Conflict of interest Vincenzo Mangialardi, Giuseppe Macchitella, Rita Vitobello, Antonella Teofilo, Nicola Cavalli, Caterina Lapucci, and Elisa Idini declare no competing financial or non-financial interests related to the content of this article. Jessica Frau reports relationships with Biogen, Bristol Myers Squibb, Novartis, Sanofi-Genzyme, Merck, Teva, and Alexion, including advisory board participation, consultancy activities, and speaker honoraria. Pietro Iaffaldano has received honoraria for lecturing, participation in advisory boards, and/or travel expenses for attending congresses and meetings from Almirall, Biogen Idec, Merck Serono, Mylan, Novartis, Roche, Sanofi-Genzyme, and Teva. Paola Cavalla has received honoraria for consultancy or speaking activities from Alexion, Biogen, Bristol Myers Squibb, Merck, Novartis, Sanofi, and Roche. Maria Matilde Inglese has received personal compensation for consulting, serving on scientific advisory boards, or speaking activities from Alexion, Biogen, Bristol Myers Squibb, Janssen, Merck, Novartis, Roche, and Sanofi-Genzyme. Eleonora Cocco has received honoraria for consultancy or speaking activities from Bayer, Biogen, Novartis, Sanofi, Merck, Teva, Roche, Bristol Myers Squibb, Janssen, and Alexion. Damiano Paolicelli has received honoraria for advisory board membership and speaking activities, travel support, research grants, consulting fees, or clinical trial support from Biogen, Bristol Myers Squibb–Celgene, Sanofi-Genzyme, Merck, Novartis, and Roche. All declared interests are unrelated to the conduct and reporting of the present study.

Ethics approval This retrospective multicenter study was conducted in accordance with the ethical standards of the institutional and national research committees and with the principles of the 1964 Declaration of Helsinki and its later amendments. This study protocol was approved by the Local Ethics Committee of the University of Bari 'Aldo Moro' (Comitato Etico Territoriale AOU Consorziale Policlinico di Bari) and by the Ethics Committees of the participating centers. Ethical approval was obtained at each participating center in accordance with national regulations for retrospective studies. This was a retrospective observational study and therefore did not require prospective trial registration.

Consent to participate Written informed consent to participate in the study was obtained from all individual participants included in the study.

Consent for publication Not applicable. The manuscript does not contain identifiable individual data.

Data availability The datasets generated and/or analyzed during the current study are not publicly available due to data protection and privacy regulations but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contributions Damiano Paolicelli contributed to the study concept and design. Vincenzo Mangialardi and Giuseppe Macchitella contributed to the analysis and interpretation of the data and drafted the manuscript. Rita Vitobello, Antonella Teofilo, Nicola Cavalli, Caterina Lapucci, Marco Vercellino, Elisa Idini, Jessica Frau, Pietro Iaffaldano, Paola Cavalla, Maria Matilde Inglese, and Eleonora Cocco contributed to data acquisition and interpretation and critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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