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Ocrelizumab as first-line therapy in highly active relapsing-remitting multiple sclerosis

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ABSTRACT

In recent years, early use of highly effective disease modifying immunotherapies in relapsing-remitting multiple sclerosis (RRMS) demonstrated superior efficacy in preventing disability progression. For this study, we investigated ocrelizumab as first line therapy of RRMS in a monocentric, retrospective study. In our outpatient clinic, ocrelizumab was administered as first-line therapy in 33 patients with an anticipated highly active disease course. Patients were re-evaluated clinically every 6 months and at least annually with cranial magnetic resonance imaging (MRI), with a mean follow-up period of 27 months. Subgroup analyses were conducted based on age, sex, disease duration, and disability as measured by EDSS at initiation of therapy. Ocrelizumab therapy was administered within the first year of diagnosis. The median EDSS at the time of ocrelizumab initiation was 2.5, with male patients showing higher disability compared to the females. The annualized relapse rate (ARR) decreased from 2.24 to 0.058 during the observation period. EDSS remained stable throughout the therapy period for the entire cohort. Starting treatment earlier and at a lower initial EDSS correlated with a better outcome. Gender and age had no impact on the therapeutic efficacy. The most common infusion related reactions included fatigue (25 %) and headaches (9 %). Mild infections occurred in 21 % of patients. These data highlight the role of ocrelizumab as an effective first-line therapeutic approach for patients with highly active RRMS.

1. Introduction

MS is a demyelinating autoimmune inflammatory disorder characterized by a chronic degenerative course [1], ultimately leading to deterioration in patient disability, irrespective of the specific disease subtype, if not adequately treated [2]. Research during the past decade added evidence to the paramount importance of timely therapeutic intervention to prevent or attenuate disability in MS [3–5].

The immunotherapy of MS has witnessed significant advancements with the introduction of"higher-efficacy" DMTs, like cladribine, sphingosine-1-phoposhate modulators, natalizumab and B cell depleting antibodies including ocrelizumab. In particular B cell directed therapeutic approaches have demonstrated superior potency in reducing relapse activity, disability progression and irreversible brain atrophy in contrast to the lower-efficacy counterparts, such as interferon-β or teriflunomide [6,7]. However, highly effective therapies may potentially lead to serious adverse events. Recent guidelines and studies increasingly advocate for the early initiation of high-efficacy DMTs in the management of MS, particularly for patients with highly active disease. This shift away from the traditional "escalation therapy" approach is based on accumulating evidence that early, aggressive treatment with high-efficacy medication may more effectively prevent long-term disability progression [5,8,9]. The "hit-hard-and-early" strategy is supported by registry data and clinical studies that indicate better long-term outcomes when high-efficacy treatments are started early in the disease course compared to waiting for the disease to worsen under less effective therapies [9,10]. This approach - especially as a part of "induction therapy" in patients at risk for rapid accumulation of disability - is key to

Abbreviations: MS, Multiple Sclerosis; RRMS, Relapsing Remitting Multiple Sclerosis; PPMS, Primary Progressive Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis; EDSS, Expanded Disability Status Scale; DMTs, Disease Modifying Therapies; ARR, Annual Relapse Rate; IRR, infusion related reaction; cMRI, cranial Magnetic Resonance Imaging; FLAIR, Fluid-Attenuated Inversion Recovery; US, United States; EU, European Union; FDA, Food and Drug Administration; EMA, European Medicines Agency)..

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slow or even prevent clinical deterioration over time [11,12].

Ocrelizumab was first approved by the US"Food and Drug Administration" (FDA) in March 2017 [13]. In the EU, ocrelizumab has been approved since 2018 [14] for the treatment of adults with RRMS with active disease, defined by clinical or imaging features, and for the treatment of adults with early PPMS.

Ocrelizumab is a humanized monoclonal anti-CD20 antibody that targets the CD20 marker on B-lymphocytes. B-cells bound to ocrelizumab are destroyed through antibody-dependent cell-mediated cytotoxicity and to a lesser extent by complement-dependent cytotoxicity [15–17].

While showing excellent efficacy in terms of reduction of relapse frequency and attenuation of disability, ocrelizumab also had favorable tolerability and an acceptable side-effect profile, leading to a reduced number of treatment discontinuations [7,18]. Currently, both research and clinical practice indicate that ocrelizumab is predominantly used as a higher-potency treatment option when patients are escalated from less potent immunomodulatory therapies in MS management.

In this retrospective, monocentric study, we present data from a treatment-naïve patient cohort receiving ocrelizumab as first-line therapy for highly active disease courses to examine both the efficacy and tolerability in a real-world setting. While the necessity of early and effective therapy in highly aggressive disease courses is increasingly recognized, there is a critical need for information on how these treatment approaches function in real-world clinical practice.

2. Methods

2.1. Study design

This study is a monocentric, retrospective data analysis using real-world data of RRMS patients treated at our academic MS Outpatient Clinic at the University Hospital of Regensburg. Ocrelizumab is fully approved by the EMA for relapsing forms of MS when disease activity is demonstrated by clinical or MRI features. Clinical activity is defined as having at least two relapses within the prior two years or one relapse within the prior year and an EDSS between 0 and 5.5, [19]. The treatment decision for patients included in our study was made as part of routine clinical care, adhering to standard prescribing guidelines and local regulatory approvals. Data were collected retrospectively between April 2018 and March 2024. The study was approved by the local Ethics Committee (24–3950-104).

Inclusion criteria were: (1) RRMS-patients without previous disease modifying therapy and ocrelizumab as the first line therapy, (2) follow-up of at least 1 year (with <4 weeks of flexibility in 6-month infusion intervals); (3) availability of relevant clinical data at baseline and at follow-up visits. Exclusion criteria were (1) primary disease progression, (2) follow-up less than 1 year and (3) lack of essential clinical data at either the initial assessment or subsequent evaluations.

The definition of a highly active disease course is still controversially discussed, and there is currently no consensus on the clinical or imaging criteria [12,20–23]. However, commonly proposed definitions include features such as two or more relapses within one year, poor recovery despite escalated relapse therapy, multiple contrast-enhancing and FLAIR lesions on cerebral MRI, and/or symptomatic infratentorial or spinal lesions.

We divided our cohort into subgroups to determine if any particular patient categories might experience exceptional benefits from the treatment approach. Apart from sex, subgroups were defined based on age, EDSS score at baseline (before therapy onset) and time to therapy initiation. The time to therapy initiation was defined as time between the first manifestation of disease and initiation of ocrelizumab treatment. For setting cut-offs according to age and therapy initiation we set thresholds based on the demographic distribution within our cohort, as it provided a balanced stratification of the study population. As the age cut-off, we selected 35 years and as the therapy initiation time cut-off we selected 12 months. The median EDSS of the total cohort was also used as cut-off for subgroup analyses (EDSS 0–2.5 versus EDSS 3.0 or higher). Of note, reaching an EDSS score of 3.0 or higher is a clinically significant threshold influencing the risk for future disease progression [24]. To stratify cohorts, EDSS thresholds of 2.0 to 3.5 are commonly applied across various studies [25–27].

Ocrelizumab was applicated consistent with standard dosing protocols beginning with two 300 mg infusions, given two weeks apart. The date of the first infusion was defined as the baseline. Subsequent infusions were performed every 6 months, allowing for a flexibility of less than 4 weeks, administered according to the prescribed infusion protocol [18,28].

2.2. Clinical variables

MS related disability was quantified using the EDSS, which was evaluated by certified physicians. Disability progression at the most recent follow-up was characterized by any 0.5-point (or higher) increase from the baseline EDSS.

The annual relapse rate (ARR) was computed as the total number of relapses in each period divided by the total number of person-years in that period [29]. To calculate the ARR before therapy, we collected the relapse count for the one-year period immediately preceding the initiation of ocrelizumab therapy. For the calculation of ARR during therapy, we included all patients for their entire observation period while undergoing treatment with ocrelizumab. The duration of observation varied among patients, reflecting the heterogeneity in treatment initiation dates and follow-up periods.

2.3. MRI variables

Standard MRI assessment for all patients included T1, T2, FLAIR, and contrast-enhanced sequences, with cerebral and, if clinically indicated, spinal imaging conducted at initial diagnosis and during follow-up for highly active MS.

For our study, MRI data were extracted from reports provided by neuroradiologists and expert neurologists. We evaluated FLAIR lesions and contrast-enhancing lesions, as well as lesion localization, categorized based on their location as supratentorial (including periventricular, subcortical, and juxtacortical regions), infratentorial, or spinal.

2.4. Analysis of tolerability and adverse events

Side effects were collected from medical records and also included ocrelizumab infusion related reactions (IRR). For adverse event reporting, an exposure-adjusted incidence rate was calculated due to the multiple administrations without cumulative effects. Adverse events were reported as the number of events per 100 infusions rather than per patient to account for varying numbers of treatments per individual. This method was calculated by dividing the total number of adverse events by the total number of administered infusions, multiplied by 100 to generate a standardized rate [30,31]. In cases with more frequent infections under treatment, a patient side analysis was, in which the number of infection events was normalized to each patient's individual exposure. This approach allowed for a more precise assessment of infection risk on a per-patient basis.

2.5. Statistics

Data analysis was executed using the Python programming language. Standard Python libraries for data science, including NumPy, pandas, seaborn, matplotlib, and scikit-learn, were utilized. Statistical analyses encompassed the chi-square test, Friedman's chi-square test, Fisher's exact test, the Wilcoxon test to compare two paired groups and students *t*-Test, where appropriate. Statistical significance in our results is demonstrated at the following levels: $*p < 0.05$ (significant), $**p < 0.01$

(highly significant), ***$p < 0.001$ (very highly significant), and ****$p < 0.0001$ (extremely significant).

3. Results

3.1. Baseline characteristics

From a comprehensive cohort of approximately 1000 multiple sclerosis (MS) patients encompassing both outpatient and inpatient settings, we identified 191 individuals currently receiving ocrelizumab therapy. Among these, 38 patients had been prescribed ocrelizumab as the first-line disease modifying therapy. 33 patients of these had a follow-up period of at least one year and were included in the present study. The cohort comprised 20 females (Mean age 32.2 ± 11.5) and 13 males (Mean age 40.7 ± 14.2). The median EDSS score for the entire cohort was 2.5 points, with male patients showing significantly greater disability (Median EDSS = 3.0) compared to the female cohort (Median EDSS = 2.0, *t*-Test $p = 0.018$). The mean follow-up duration was 27.7 months (±16.4), with a minimum observation period of 1 year for all included patients. The mean age of the patients at therapy initiation was 35.5 ± 13.1 years (mean ± standard deviation, SD). The mean age at symptom onset was 31.7 ± 11.8 years, with the youngest patient being 16 and the eldest 56 years old. The mean age at first diagnosis was 35.4 ± 12.6 years. The mean time interval from initial diagnosis to the initiation of ocrelizumab therapy was 11.5 months (± 25.4 months SD). (Table 1).

All patients received a standard dose of 600 mg ocrelizumab except two patients, who received a reduced ocrelizumab dosage of 300 mg every 6 months from baseline due to a BMI below 20.

Overall, the cohort reflects a typical real-world RRMS cohort and shares key characteristics with large world-wide registries including the MSBase Registry, Swedish MS Registry, Italian MS Registry, and the OFSEP (Observatoire Français de la Sclérose en Plaques) registry. These similarities encompass demographic data collection, longitudinal clinical assessments, and comprehensive treatment outcome monitoring.

3.2. Effect of ocrelizumab on relapse rate

Prior to the initiation of ocrelizumab therapy, the mean annual Relapse Rate (ARR) for the entire cohort was 2.24 (range 1 to 4 relapses) in the year preceding treatment. Following the initiation of ocrelizumab, ARR was markedly reduced to a rate of 0.058, representing a highly statistically significant reduction of 97 % in relapse rate ($p < 0.0001$). The ARR was calculated during the observation period of up to 5 years, which was completed by 7 patients. Notably, subgroup analyses demonstrated that this significant reduction in relapse rate was consistent across all patient subgroups, regardless of baseline characteristics. (Fig. 1).

Table 1
Baseline characteristics.

Baseline data	Mean	Details
Age at therapy onset	35.5 ± 13.1	Absolute n: 33
Age at first manifestation (FM)	31.7 ± 11.8	Min.- 16 years/max.- 56 years
Age at first diagnosis (FD)	35.4 ± 12.6	Min.- 16 years/max.- 59 years
Time period between FM and FD (months)	27.3 ± 55.9	Min.- 0 month/max.- 23 years
Time period between FD and therapy initiation (TI; months)	11.5 ± 25.4	Min.- 1 month/max.- 9 years
Time period between FM and TI (months)	39.3 ± 74.0	Min.- 1 month/max.- 32 years
Male age	40.7 ± 14.2	Median EDSS 3.0 (min.-1.0/max.-7.0)
Female age	32.2 ± 11.5	Median EDSS 2.0 (min.-1.0/max.-4.5)
Duration of therapy/observation time	27.7 ± 16.4	Min.- 1 year/max.- 5 years
EDSS before therapy initiation	2.8 ± 1.5	Median: 2.5 (min.- 1.0/max.-7.0)
Annualized relapse rate before therapy	2.24 ± 0.83	Min.- 1.0/max- 4.0

3.3. Effect of ocrelizumab on MRI

Pre-treatment MRI data was available for all patients and for 31 patients during follow-up. Initial scans showed supratentorial lesions in all 33 patients, infratentorial in 27, and spinal in 26 patients. 19 patients showed gadolinium-enhancing lesions. This pattern is well in line with the diagnosis of highly active MS in the cohort.

During follow-up, ten patients developed new lesions (7 periventricular, 3 spinal, 1 infratentorial). Importantly, 7 of these cases likely developed these new lesions before ocrelizumab treatment was fully effective, as lesions were detected within the first 3–6 months of therapy during initial control MRI. Three patients showed new lesions (two patients with contrast enhancement and one without) later on during follow-up.

Treatment reduced contrast-enhancing lesions from 58 % (19/33) to 6 % (2/31) of patients, equaling a highly significant reduction of 94 % ($p < 0.0001$, Fisher's exact test). The development of new FLAIR lesions decreased by 90 %, with a significant reduction in formation of new lesions across all anatomical regions ($p < 0.0001$). (Table 2).

3.4. Effect on clinical outcomes and EDSS

The median EDSS was 2.5 at baseline and showed a non-significant decrease to 2.0 after up to three years of follow-up. Further analysis of disability progression showed a stable disease course or an improvement in 82 % of patients.

For a further subgroup analysis, a cut-off of 12 months after initial MS manifestation was determined. Eighteen patients started ocrelizumab within 12 months of symptom onset (baseline EDSS 2.0). There was observed a non-significant trend toward improvement, indicating overall EDSS stability (Fig. 2A). Thirteen patients started ocrelizumab >12 months after symptom onset (median EDSS 3.0), showing

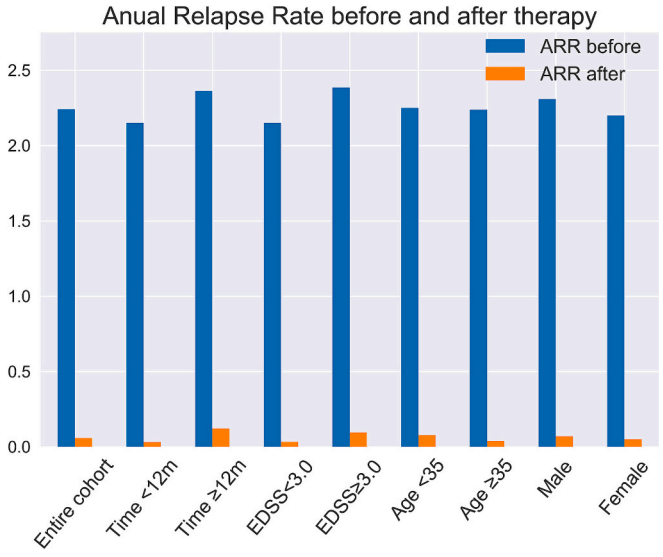

Fig. 1. Annualized relapse rates (ARR) pre- and post-therapy initiation. Before ocrelizumab initiation, the ARR in the entire cohort was 2.24. Post-treatment initiation, the relapse rate decreased to 0.058 (Wilcoxon signed ranked test: $p < 0.0001$). The ARR reduction was highly significant in all subgroups ($p < 0.0001$).

Table 2
MRI lesion load before and after therapy.

	Before ocrelizumab		After ocrelizumab			
Lesion type	Number of patients	%	Number of patients	%	Reduction %	*p*-value
Total amount of patients with new MRI lesions	33	100	3	9.68	90.32	<0.0001
Periventricular, Subcortical/Juxtacortical	33	100	2	6.45	93.55	<0.0001
Infratentorial	27	81.82	0	0	100	<0.0001
Spinal	26	78.79	1	3.23	95.91	<0.0001
Contrast-enhancing	19	57.58	2	6.45	93.55	<0.0001

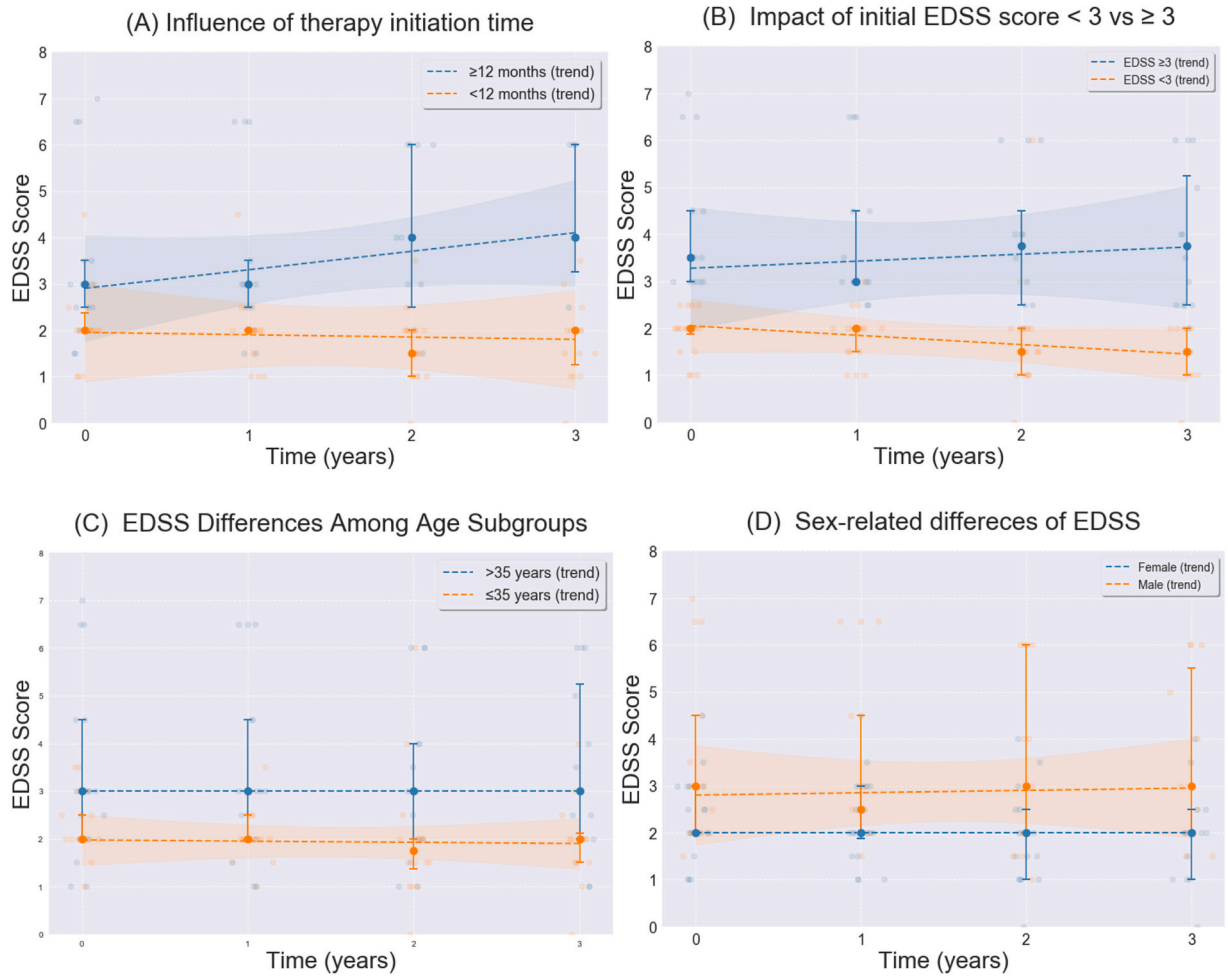

Fig. 2. Subgroup analysis of EDSS development over a mean 3-year observation period. Linear regression trend (dashed line) with median values (dark points), quartiles (error bars), individual values (light points), and 95 % confidence interval (shaded area) are shown.
(A) Patients with a therapeutic delay from symptom onset to start of ocrelizumab for more than 12 months showed a slight worsening of EDSS, while patients with therapy initiation in the first 12 months remained stable.
(B) Patients with an initial EDSS score of less than 3.0 showed a significant reduction of disability over time ($p = 0.03$). Conversely, the subgroup with a higher initial EDSS score ≥3.0 did not show significant changes over time.
(C) There were no significant differences in EDSS progression between younger and older patients during treatment, despite higher baseline EDSS in the older group.
(D) Male patients showed a significantly higher EDSS at baseline ($p = 0.018$). Over three years, both subgroups remained stable and did not show significant changes in their EDSS score.

significantly higher baseline EDSS compared to early-treatment group ($p = 0.019$). In this subgroup, an increase of EDSS to a median of 4 was observed, however, this change was not statistically significant (Fig. 2A).

To assess the grade of disability, our cohort was divided according to EDSS. 20 patients with baseline EDSS <3.0 (median 2.0) showed a statistically significant EDSS reduction after three years ($p = 0.03$). In contrast, 13 patients with baseline EDSS ≥3.0 (median 3.5) showed a slight increase of the EDSS of 3.75 ($n = 12$), without statistical significance. (Fig. 2B).

At baseline, age and sex differences were significant: patients older than 35 years had higher median EDSS compared to younger patients (3.0 vs. 2.0, $p = 0.037$), as did males compared to females (3.0 vs. 2.0, $p = 0.018$). Treatment effectiveness showed no significant differences between groups. (Fig. 2C, D).

Analysis of EDSS functional system scores at one-year follow-up showed overall stability across most domains, while sensory function showed significant improvement ($p = 0.02$, Fig. 3).

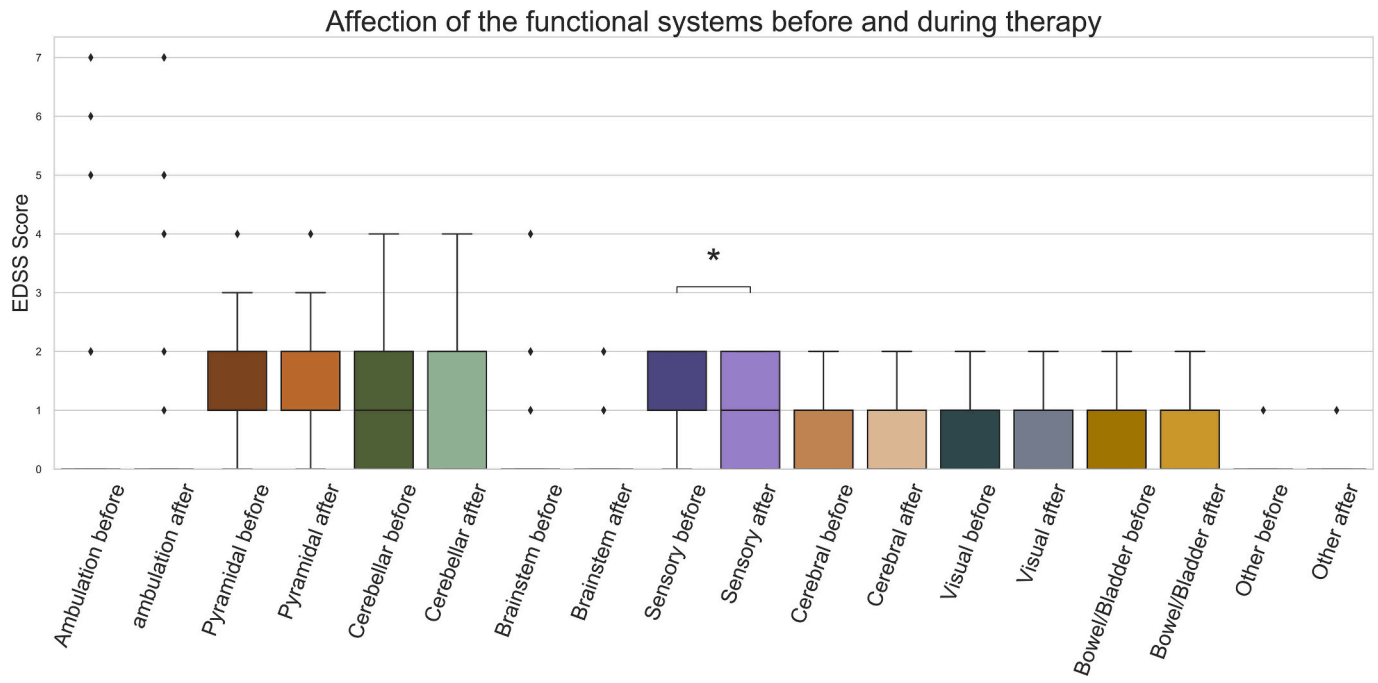

Fig. 3. Comparison of functional systems before and one year after initiating ocrelizumab therapy: The rectangular boxes represent the Interquartile Range - the range between the 25th and 75th percentiles. The horizontal line inside the box is the median value. Each pair of boxes (before/after) represents one functional system in related color shades. Whiskers extend to the minimum (0) and maximum values of up to four. Diamond-shaped points beyond the whiskers are outliers. Among the eight functional systems, only the sensory function demonstrated a statistically significant decrease post-treatment (**P*-value: 0.024). The remaining seven systems exhibited no notable alterations after therapy.

3.5. Tolerability and adverse events

Of 118 administered infusions, 45 % were completely free of IRR. The most common IRR included fatigue (24.6 %) and headaches (8.5 %). Nausea occurred in 3.4 % and tachycardia and hypertension in 2.5 % of cases each. Less frequent adverse events were dizziness and swelling of joints or face (1.7 % each). Single cases included leukopenia, rhinitis, hair loss, joint pain, and sunlight sensitivity. Infections occurred in 21 % of patients, were mild in all cases, and included respiratory tract infections, lower urinary tract infections, and a single case of uveitis.

4. Discussion

In this real-world, single-center, retrospective study of 33 treatment-naïve RRMS patients with highly active disease, a first-line therapy with ocrelizumab demonstrated remarkable efficacy. ARR showed a reduction of 97 %. This marked reduction highlights a robust therapeutic response, particularly in a cohort characterized by high initial disease activity with more than two relapses per year prior to disease modifying therapy. The observed efficacy of ocrelizumab in our cohort is consistent with results from pivotal and real-world studies. Albeit different in study design, our data are well in line with previous results of the OPERA I and II trials, where ocrelizumab achieved ARR reductions of 46 % and 47 % respectively, with an ARR of 0.16 after 2 years of treatment [6]. Smoot et al. [36] reported an ARR of 0.09 in real-world settings. Zhu et al. [37] highlighted similar efficacy in patients transitioning from natalizumab, with an ARR of 0.12.

In randomized controlled trials, the majority of participants were treatment-naïve, which does not accurately reflect the real world population. This discrepancy has been evident in numerous real-world studies following approval of new treatments for multiple sclerosis, where the observed effectiveness was often lower than in clinical trial settings. [32–38].

The observed treatment response in our real-world, unselected population demonstrates a significantly higher benefit in terms of annualized relapse rate (ARR) reduction compared to randomized controlled trials. Recent publication of the Open-Label Extension of Nine-Year Data from the OPERA studies demonstrated a reduction in annualized relapse rate to 0.05, corroborating our findings [5].

MRI data further substantiated the clinically observed stability, showing a 90 % reduction in new FLAIR lesions and a 94 % reduction in gadolinium-enhancing lesions, indicating a profound suppression of radiological disease activity. These observations are consistent with the results of both pivotal trials and real-world evidence. Comparable efficacy was reported by Kappos et al. [30], who demonstrated an 89 % reduction in gadolinium-enhancing lesions and overall radiological disease activity of 16 %, similar to our finding of 10 %. The OPERA I and II trials further substantiated this therapeutic effect, showing 94 % and 95 % reductions in new or enlarging T2 lesions compared to interferon beta-1a [7]. Additional real-world evidence from Smoot et al. (2021) [39] demonstrated minimal radiological activity, with gadolinium-enhancing lesions observed in only 1.4 % of patients across various MS phenotypes. However, methodological heterogeneity and diverse patient populations necessitate cautious interpretation of cross-study comparisons.

The median EDSS score improved by 0.5 points over three years, although this trend lacked statistical significance. Stability or improvement in EDSS was observed in 82 % of the cohort. Moreover, early treatment initiation (within 12 months of symptom onset) was associated with lower disability, as these patients demonstrated lower baseline EDSS and a non-significant trend toward improvement. In contrast, delayed treatment initiation (>12 months post-symptom onset) was associated with higher baseline EDSS scores and a slight, non-significant trend toward EDSS progression. The stabilization of EDSS scores in both groups, regardless a delayed treatment timing, underscores ocrelizumab's efficacy in maintaining functional stability, though the data suggests superior outcomes with earlier intervention. These findings support the "window of opportunity" hypothesis, emphasizing the importance of early intervention to minimize long-term disability [9,40]. Subgroup analysis using an EDSS cut-off of 3.0 revealed that

patients with lower baseline disability exhibited significantly better responses, underscoring the value of starting treatment before moderate disability levels are reached [24]. Furthermore, 86.6 % of the patients in the CASTING study showed steady or improved EDSS after two years, which is consistent with the observed stability rate after three years in this study. Additionally, the CASTING study found that 86.6 % of patients experienced stable or improved EDSS scores over two years [41], aligning with our three-year stability rate of 82 %. Moreover, a post-hoc analysis of the OPERA trials highlighted that the treatment effect of ocrelizumab on EDSS progression was sustained over time, with continued benefits observed beyond the initial treatment period [42].

Younger patients and women demonstrated significantly lower baseline EDSS compared to older and male patients, though treatment response remained consistent across demographic subgroups [43,44].

After one year of treatment, significant improvement was observed in the sensory system of the EDSS, with near-significant amelioration in ambulation. This improvement in the sensory function score may be due to the fact, that disturbances of sensation are among the more sensitive deficits of MS and are often reported early in the disease course [45]. Moreover, spinal disease activity causing sensory deficits, is well controlled by B cell depletion. Evidence for ocrelizumab's impact on functional systems has been demonstrated across MS forms, with the ORATORIO trial showing reduced progression of upper extremity impairment in PPMS [46], and analyses revealing enhanced protection against disability progression in patients at risk of SPMS, particularly those with elevated pyramidal functional system scores [47]. While these findings suggest ocrelizumab's protective effect on specific functional systems, the limited data regarding functional system outcomes in RRMS warrants further investigation.

Analysis of treatment discontinuation revealed that one patient ceased therapy due to relapse and clinical progression, a rate consistent with findings from Smoot et al. (2023) [39], who documented therapy discontinuation in 4.2 % of cases due to disease activity.

Safety outcomes in our cohort were consistent with expectations from pivotal trials [7,46,48]. While fatigue was the predominant infusion-related reaction, isolated cases of infection susceptibility and leukocytopenia aligned with known long-term safety profiles [49]. The observed discontinuation rate of 3 % (one case) due to recurrent infections parallels the adverse event-related discontinuation rates reported in OPERA I (3.2 %) and OPERA II (3.8 %) [7].

Our study faced inherent limitations in follow-up duration and sample size, which further decreased during follow-up, thereby limited statistical power and generalizability of findings. The varying treatment initiation dates resulted in different follow-up durations for each patient. Therefore, results of our regression analyses may have reduced validity. This is consistent with similar real-world studies, such as the Sardinian cohort (67 treatment-naive patients in cohort of 421 patients) [50] and Swiss population study (75 treatment-naive patients in cohort of 235 patients) [51] which faced comparable challenges in maintaining consistent long-term follow-up.

Further study limitations include incomplete post-treatment imaging data and inherent EDSS limitations in capturing upper extremity and cognitive changes [52,53]. Large-scale studies are needed to evaluate the long-term efficacy and safety of ocrelizumab as a first-line therapy in real-world setting. Direct comparisons between studies should be interpreted with caution due to methodological heterogeneity and diverse patient populations, our study is distinguished by its focus on treatment naïve RRMS patients exhibiting highly active disease.

Recent research aligns with our findings and emphasizes early therapeutic intervention in MS management with high-efficacy DMTs outperforming traditional treatments [54–56] [5]. The "hit hard and early" strategy has shown superior long-term outcomes [9,42,57].

5. Summary and conclusions

In the present study of 33 patients with highly active RRMS treated with ocrelizumab as a first line therapy we show that ocrelizumab is highly effective in reducing inflammatory disease activity (ARR, MRI) and progression (EDSS), especially if started early. Subgroup analyses revealed significant EDSS reduction in patients with baseline EDSS <3.0. We observed no significant gender and age-related differences regarding therapy efficacy. Side effects were within the expected range. Thus, we conclude that the beginning of ocrelizumab – if indicated by a highly active MS course – should not be delayed.

CRediT authorship contribution statement

Tamar Kvartskhava: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **David Freudenstein:** Writing – review & editing, Resources, Project administration, Methodology, Conceptualization. **Nicolas Sarmiento:** Visualization, Validation, Software, Formal analysis. **Klemens Angstwurm:** Writing – review & editing, Validation, Resources. **Ralf Linker:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Conceptualization. **De-Hyung Lee:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

TK, DF, NS We declare that there are no conflicts of interest regarding the research, authorship, and/or publication of this article. We have not received any financial support or other benefits from any commercial sources, nor do we have any personal or professional affiliations that could be perceived as influencing the results or interpretation of the findings. All research was conducted independently, and we remain committed to maintaining transparency and integrity in our work.

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