

Ocrelizumab initiation in patients with MS

A multicenter observational study

Erik Ellwardt, MD, Leoni Rolfes, MD, Julia Klein, Katrin Pape, MD, Tobias Ruck, MD, Heinz Wiendl, MD, Michael Schroeter, MD, Frauke Zipp, MD, Sven G. Meuth, MD, Clemens Warnke, MD, and Stefan Bittner, MD

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Correspondence

Dr. Ellwardt
erik.ellwardt@unimedizin-mainz.de

Abstract

Objective

To provide first real-world experience on patients with MS treated with the B cell–depleting antibody ocrelizumab.

Methods

We retrospectively collected data of patients who had received at least 1 treatment cycle (2 infusions) of ocrelizumab at 3 large neurology centers. Patients' characteristics including pre-medication, clinical disease course, and documented side effects were analyzed.

Results

We could identify 210 patients (125 women, mean age \pm SD, 42.1 ± 11.4 years) who had received ocrelizumab with a mean disease duration of 7.3 years and a median Expanded Disability Status Scale score of 3.75 (interquartile range 2.5–5.5; range 0–8). Twenty-six percent of these patients had a primary progressive MS (PPMS), whereas 74% had a relapsing-remitting (RRMS) or active secondary progressive (aSPMS) disease course. Twenty-four percent of all patients were treatment naive, whereas 76% had received immune therapies before. After ocrelizumab initiation (median follow-up was 200 days, range 30–1,674 days), 13% of patients with RRMS/aSPMS experienced a relapse (accounting for an annualized relapse rate of 0.17, 95% CI 0.10–0.24), and 5% of all patients with MS experienced a 12-week confirmed disability progression. Treatment was generally well tolerated, albeit only short-term side effects were recorded, including direct infusion-related reactions and mild infections.

Conclusions

We provide class IV evidence that treatment with ocrelizumab can stabilize naive and pretreated patients, indicating that ocrelizumab is an option following potent MS drugs such as natalizumab and fingolimod. Further studies are warranted to confirm these findings and to reveal safety concerns in the longer-term follow-up.

Classification of evidence

This study provides Class IV evidence that for patients with MS, ocrelizumab can stabilize both treatment-naive and previously treated patients.

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→ Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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From the Focus Program Translational Neurosciences (FTN) and Immunology (FZI) (E.E., K.P., F.Z., S.B.), Rhine Main Neuroscience Network (rmn²), Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz; Department of Neurology (L.R., T.R., H.W.), University of Muenster; Department of Neurology (J.K., M.S., C.W.), Faculty of Medicine and University Hospital Cologne, University of Cologne; and Department of Neurology (S.G.M.), Institute of Translational Neurology, University of Muenster, Germany.

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Glossary

ARR = annualized relapse rate; **aSPMS** = active secondary progressive MS; **EDSS** = Expanded Disability Status Scale; **PML** = progressive multifocal leukoencephalopathy; **PPMS** = primary progressive MS; **RRMS** = relapsing-remitting MS.

The humanized anti-CD20 B cell–depleting antibody ocrelizumab has been approved for treatment of MS by the European Medicines Agency in 2018 following positive results in phase 3 studies for the relapsing-remitting (RRMS) and the primary progressive (PPMS) disease course.^{1,2} Ocrelizumab is the first-ever approved treatment option for patients with active PPMS. The concept of B-cell depletion for treatment of MS is not new.^{3,4} There had already been evidence from phase II clinical studies that assessed rituximab in relapsing and primary progressive MS,^{5,6} another CD20 B cell–depleting antibody.⁷ This was further supported by observational studies, e.g., from the Swedish registries, indicating effect sizes similar to those of the later ocrelizumab studies.^{8,9} Ongoing disease activity, intolerable side effects, or safety concerns (progressive multifocal leukoencephalopathy [PML])¹⁰ are possible situations when a treatment has to be stopped and switched to an alternative drug. The cumulative risk for re-emerging disease activity at year 1 after cessation of natalizumab treatment was estimated to be around 45% (95% CI 0.41–0.49)¹¹ and 26% at month 6 for fingolimod^{12,13} arguing for a prompt restart of an alternative disease-modifying drug.

Previously, a Swedish retrospective study has shown that the consecutive treatment with rituximab following natalizumab is safe and minimizes the risk of a clinical relapse (1.8% within 1.5 years).¹⁴ So far, there are no data available for the benefits and risk of switching to ocrelizumab following natalizumab or fingolimod, justifying this retrospective real-world data analysis, in the absence of prospective class 1 evidence.

Methods

Patients and data acquisition

We analyzed data of all patients with MS who had received at least the initial treatment of 2 ocrelizumab cycles (300 mg and with an interval of 2 weeks) at the neurology departments of the universities of Mainz, Münster, and Cologne (all Germany). The evaluations of clinical relapses or disease progression during treatment switch (washout period) and after ocrelizumab initiation were assessed by reviewing medical reports and letters until June 1, 2019. The median follow-up of the cohort was 200 days. The analysis of this retrospective study data was approved by the respective local ethics committees.

Definition of relapse or progression

A relapse was defined as an acute or subacute evolution of a new symptom or a significant deterioration of a previously existing deficit lasting for at least 24 hours and which was not due to infections or other non-neurologic diseases. All patients in this study who were classified to have a relapse had

received IV methylprednisolone or plasmapheresis. Progression was defined as a documented increase in the Expanded Disability Status Scale (EDSS) score (1-point increase if the EDSS score was equal or below 5 and 0.5-point increase if the EDSS score was above 5) confirmed after 12 weeks.

Washout time and follow-up

The washout time was defined as the time interval between the last administration of the previous treatment and the first infusion of ocrelizumab. Patients were excluded for this analysis if the washout interval was longer than 200 days, except if the previous treatment was rituximab, alemtuzumab, or mitoxantrone. Only patients with full information for treatment time points and clinical data on follow-up checks were included. A data analysis regarding the clinical development of patients following the first ocrelizumab infusion was only performed if the documented follow-up after the second ocrelizumab infusion within the first treatment cycle was at least 30 days.

Analysis

SPSS (Version 23.0) and GraphPad Prism (Version 5) were used for statistical analysis. To compare more than 2 groups, an ANOVA test was performed and considered significant with a $p < 0.05$. To compare 2 groups, a Student t test or χ^2 test was used where appropriate.

Data availability

Data are available from the authors on request.

Results

Cohort characteristics

A total of 210 (125 female and 85 male) patients, who had received the first treatment cycle of ocrelizumab, consisting of 2 separate infusions, could be identified. The mean age at ocrelizumab initiation was 39.2 years for patients with RRMS and 50.2 for patients with PPMS. The mean disease duration was 8.0 (RRMS) and 5.1 years (PPMS; see table 1 baseline characteristics compared with OPERA 1 [a study of ocrelizumab in comparison with interferon beta-1a in participants with relapsing multiple sclerosis] and ORATORIO [a study of ocrelizumab versus placebo to treat primary progressive MS]). About a quarter (55 patients, 26%) had PPMS, whereas 74% (155 patients) had RRMS or secondary progressive disease course with relapses (active SPMS or aSPMS). Twenty-four percent of ocrelizumab-treated patients were treatment-naive patients, whereas 76% had received a previous immune therapy (table 1 and figure 1A). Among the most prevalent previous immune therapies (see complete spectrum in figure 1B) were natalizumab ($n = 39$ patients), fingolimod ($n = 24$), and

Table 1 Baseline characteristics of our cohort of 210 patients with MS who were treated with ocrelizumab compared with OPERA 1 and ORATORIO

Baseline characteristics	Own cohort RRMS/ aSPMS (n = 155)	OPERA 1 OCR (n = 410)	OPERA 1 IFN (n = 411)	Own cohort PPMS (n = 55)	ORATORIO OCR (n = 488)	ORATORIO placebo (n = 244)
Female, n (%)	96 (62%)	270 (66%)	272 (66%)	96 (53%)	237 (49%)	124 (51%)
Age at first ocrelizumab, y, mean ± SD	39.2 ± 10.7	37.1 ± 9.3	36.9 ± 9.3	50.2 ± 9.1	44.7 ± 7.9	44.4 ± 8.3
Disease duration, y, mean ± SD	8.0 ± 7.1	3.8 ± 4.8	3.7 ± 4.6	5.1 ± 5.8	2.9 ± 3.2	2.8 ± 3.3
EDSS score before ocrelizumab, mean ± SD; median (IQR; range)	3.6 ± 1.9; 3.25 (2–5; 0–8)	2.9 ± 1.2; /	2.8 ± 1.3; /	4.9 ± 1.6; 5 (3.75–6; 2.5–8.5)	4.7 ± 1.2; /	4.7 ± 1.2; /
Previous immune treatment, n (%)						
Naive	25 (16%)	301 (74%)	292 (71%)	25 (45%)	433 (89%)	214 (88%)
Pretreated	130 (84%)	107 (26%)	117 (29%)	30 (55%)	55 (11%)	30 (12%)
Reason for switch to ocrelizumab, n (%)						
Clinical progress	80 (62%)	/	/	26 (87%)	/	/
Safety concerns due to PML risk	22 (17%)	/	/	0	/	/
Side effects of previous therapy	28 (21%)	/	/	4 (13%)	/	/

Abbreviations: aSPMS = active secondary progressive MS; EDSS = Expanded Disability Status Scale; IFN = interferon beta-1a; IQR = interquartile range; OCR = ocrelizumab; PPMS = primary progressive MS; RRMS = relapsing-remitting MS.

dimethyl fumarate (n = 22). The main reason why patients were switched to ocrelizumab was clinical deterioration (n = 106 patients, 66%), whereas particularly natalizumab patients were switched to ocrelizumab because of safety reasons (21 of 39 patients or 54% due to safety concerns due to PML risk). Daclizumab therapy was discontinued due to its withdrawal from the market following reports of severe side effects such as encephalitis¹⁵ and liver failure.¹⁶ Most prevalent preexisting comorbidities of treated patients comprised thyroid disease, depression, smoking, hypertension, allergic asthma, migraine, urinary incontinence, and diabetes (see full spectrum in table e-1, links.lww.com/NXI/A235).

Clinical course during treatment-free interval before ocrelizumab initiation

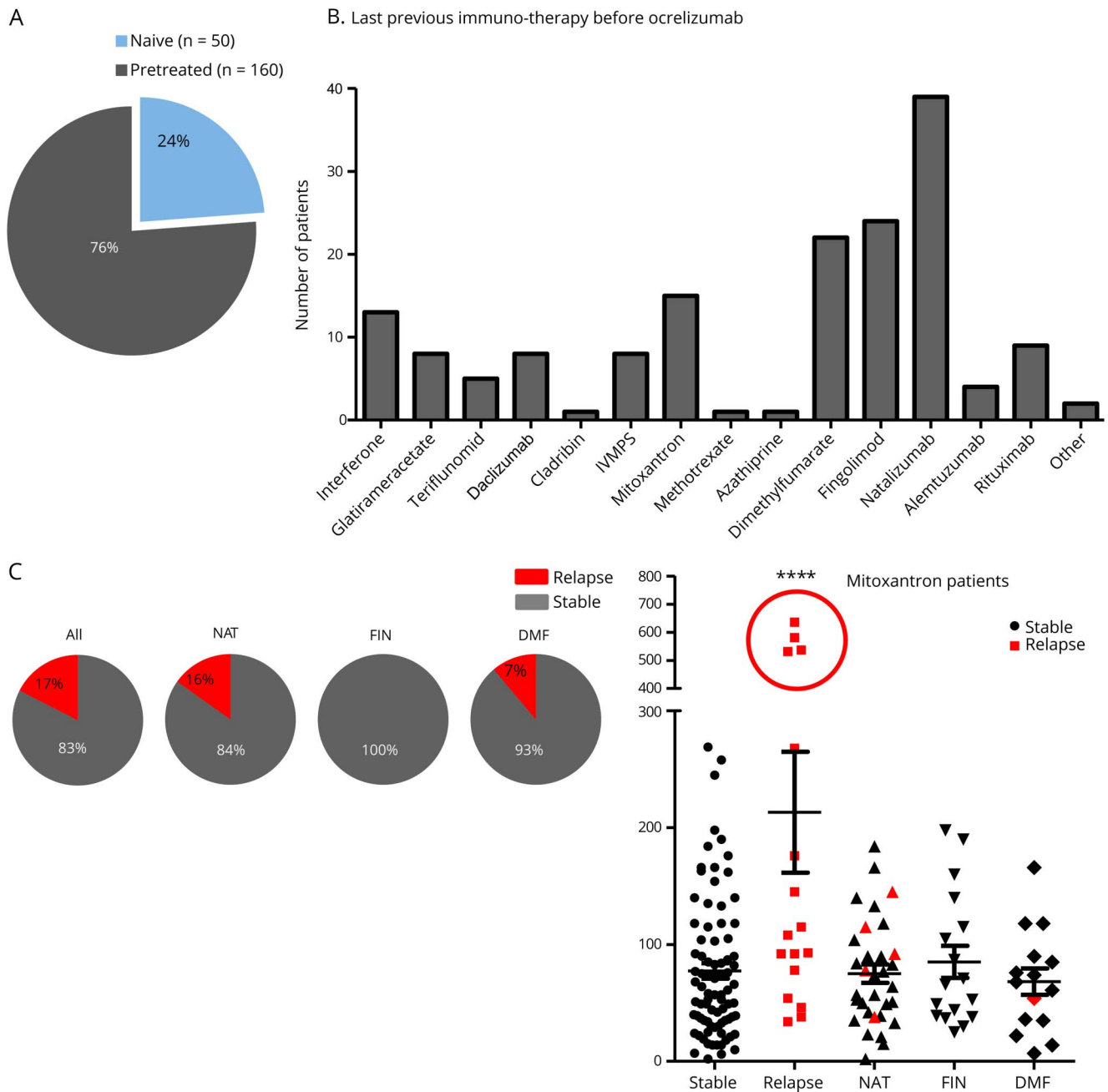
Of 160 patients who had received previous therapy, we had sufficient data to assess clinical disease course in 100 patients (all RRMS/aSPMS) during treatment-free interval before ocrelizumab initiation. Of these 100 patients, 17 (17%, 95% CI 0.095–0.245) experienced a relapse in the treatment-free interval (figure 1C, left panel). Patients who had a relapse had a significant longer washout interval than patients who were stable (figure 1C, right panel, mean ± SEM; stable: 77.5 ± 6.6 vs relapse 213.2 ± 51.7 days, *p* < 0.001, 1-way ANOVA). However, the increased washout period was biased due to 4 mitoxantrone-treated patients, who had a very long washout interval and who showed ongoing disease

activity. The subgroup analysis for natalizumab (n = 32 patients, n = 5 patients with relapse, 95% CI 0.156–0.369, washout: 75.1 ± 7.9 days), fingolimod (n = 17 patients, 0 patients with relapse, washout: 85.1 ± 13.8 days), and dimethyl fumarate (n = 15 patient, 1 patient with relapse, 95% CI 0.067–0.258, washout: 68.3 ± 11.3 days) revealed no differences among groups, both for the relapse rate and the washout interval.

Stable clinical disease course after treatment initiation with ocrelizumab

We could include 136 patients in the assessment of their clinical disease course with a median follow-up of 200 days (range 30–1,674 days). In total, 21 patients (15%, 95% CI 0.093–0.216) showed a clinical deterioration (14 relapses [10%]/7 progression [5%]) after treatment initiation with ocrelizumab (figure 2A–C). In 2 of 26 patients who were switched from natalizumab to ocrelizumab (8%, 95% CI 0–0.187), a clinical worsening (2 relapses/0 progression) was reported within a median follow-up of 209.5 days (range 105–447 days), whereas in patients following treatment with fingolimod, 3 of 15 patients (0 relapse/3 progression) were reported (20%, 95% CI 0–0.430, median follow-up 196 days, range 51–421 days). In the 15 patients pretreated with dimethyl fumarate, only 1 relapse (7%) was documented (95% CI 0–0.210, 1 relapse and no progression, median follow-up 197 days, range 74–985 days). In treatment-naive patients, clinical deterioration was noted in 4 of 31 of the patients (3

Figure 1 Pretreatment before ocrelizumab initiation and clinical assessment during treatment-free interval (washout period)



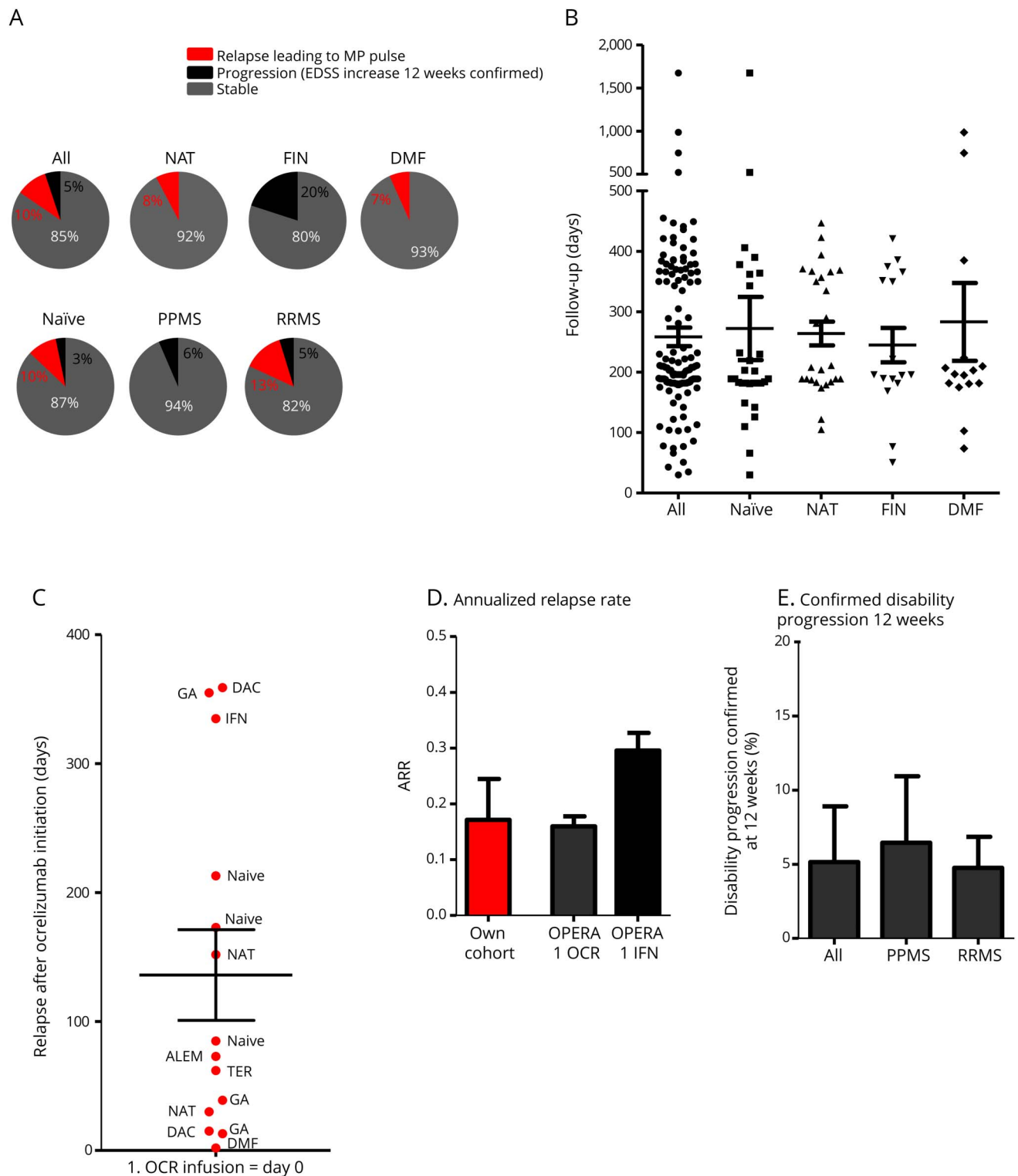
(A) Twenty-four percent of patients were treatment naive, whereas 76% of patients had received a previous medication such as interferon-beta or natalizumab (number of patients treated with MS drug before ocrelizumab in (B)). (C) Clinical disease course during the washout interval and length of washout interval for the depicted conditions. N (all) = 100 patients, n (natalizumab) = 32, n (fingolimod) = 17, and n (dimethyl fumarate) = 15. We observed significant higher washout intervals in patients who experienced a relapse ($***p < 0.001$, 1-way ANOVA, mean \pm SEM); black symbols indicate stable patients and red symbols refer to patients with a relapse during the washout period. IVMPS = IV methylprednisolone every 3 months.

relapse [10%]/1 [3%] progression), accounting for 13% (95% CI 0.004–0.254), with a median follow-up of 189 days (range 30–1,674 days). Among the 31 patients with PPMS, 2 had an EDSS progression (6%, 95% CI 0–0.156), whereas of 105 patients with RRMS, 19 showed a relapse or progression (18%, 95% CI 0.106–0.256, 14 relapses [13%], 5 progression [5%]).

Annualized relapse rate and disability progression

The symptoms of a relapse were reported after approximately 136 days (figure 2C) following the first ocrelizumab infusion. None of these patients were switched to an alternative therapy during the observational period. Taking into account that there have been 14 relapses in 105 patients with RRMS with

Figure 2 Clinical assessment after treatment initiation



(A) Overall, 15% of patients experienced a relapse (10%, n = 14) or 12-week confirmed disability progression (5%, n = 7) after ocrelizumab treatment initiation, with, e.g., 8% for natalizumab-pretreated patients (2 relapse/0 progression in 26 patients). N (all) = 136 patients, n (natalizumab) = 26, n (fingolimod) = 15, n (dimethyl fumarate) = 15, n (naïve) = 31, n (PPMS) = 31, and n (RRMS) = 105. (B) Follow-up in days of the patients (mean ± SEM). (C) The mean occurrence of a relapse (n = 14 events) was 136 days after the first ocrelizumab infusion (mean ± SEM). Each point is labeled with the pretreatment. (D) Annualized relapse rate of our cohort compared with the ocrelizumab group and interferon beta-1a group of the OPERA 1 trial (mean with 95% CI). (E) Confirmed disability progression after 12 weeks of our cohort (mean with 95% CI). ALEM = alemtuzumab; DAC = daclizumab; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFN = interferon beta-1a; NAT = natalizumab; OCR = ocrelizumab; PPMS = primary progressive MS; RRMS = relapsing-remitting MS; TER = teriflunomide.

a median follow-up of 204 days (mean follow-up = 266 days), this translates into an annualized relapse rate (ARR) of 0.17 (figure 2D, 95% CI 0.098–0.244), which is in line with previously reported phase 3 clinical trial data. Within our short observation period, we observed a 12-week confirmed disability progression in 5% of all patients (figure 2E, 95% CI 1.4–8.9%). The baseline characteristics including sex, age, disease duration, or EDSS were not different between stable patients or patients who experienced a relapse or progression (table 2).

Treatment with ocrelizumab was well tolerated

In about 22% (46 patients of 210) of the patients, any side effects were reported, most of them of mild nature (table 3). Among them, we could observe most frequently transient infusion-related side effects such as headache or tachycardia and erythema (9% of patients), which did not lead to treatment discontinuation but in some cases to a reduction of infusion speed. Minor infections such as respiratory or urinary tract infections (8%) and 2 cases of a prolonged herpes labialis infection were documented as delayed possible side effects. One patient with multiple previous therapies (glatiramer acetate, interferon-beta, and natalizumab) suffered approximately 5 months after first ocrelizumab infusion from a toxic drug-induced hepatopathy (diagnosis secured by biopsy) with slightly increased liver enzymes (2-fold above upper limit of the reference values of the laboratory) and increased cholestasis parameters such as GGT and AP (up to 10-fold above upper limit). This was the only patient who had to be temporarily discontinued in our cohort. Liver enzymes rapidly normalized and therapy with ocrelizumab could be reinitiated.

Discussion

Ocrelizumab has recently been introduced for patients with relapsing MS and early PPMS. Real-world data on the post-marketing use of ocrelizumab so far are scarce. However, results of phase 3 clinical trials may not be applicable to all patients in the approved indication due to differences in

characteristics when starting treatment. Indeed, compared with the ocrelizumab phase 3 trials OPERA 1 and 2 and ORATORIO,^{1,2} disease duration in our cohort was longer at the time of ocrelizumab initiation (8 vs 3.8 years for RRMS/aSPMS and 5.1 vs 2.9 years for PPMS), and patients were less frequently treatment naive (16% vs 74% for RRMS and 45% vs 89% for PPMS). Age and baseline EDSS score were only slightly higher compared with phase 3 trials. Nonetheless, despite these different baseline characteristics, the nature of adverse events was comparable to what has been noted during the study program. As reported,^{1,2} we mainly observed mild to moderate infusion-related reactions (9%) and mild infections (8%) in our cohort. However, the percentage of documented infusion-related reactions and infections in our cohort is clearly lower than in the phase 3 trials, which might be due to strict premedication protocols with IV methylprednisolone (250 mg), antipyretic agents, and antihistamine drugs, which were not obligatory in OPERA 1 or 2 and/or because of an underreporting by patients due to the mildness of the adverse event. Only 1 of 210 patients with MS temporarily discontinued treatment with ocrelizumab due to safety issues during the limited median observational period of around 200 days. Our study certainly does not allow conclusions on the long-term safety of ocrelizumab. In particular, rate of infections or risk of malignancies may increase over time. For example, the risk of hypogammaglobulinemia and decreasing IgM levels during the prolonged therapy might associate with an increased risk of severe infections.

Real-world experience may be of particular relevance for treatment decisions not studied during the trial period. Observational studies before registration of ocrelizumab have noted high rates of return of MS disease activity following natalizumab cessation, a subgroup that was, with 19%, the largest pretreatment subgroup of our study. In a French cohort, a relapse rate of 45% in the year following natalizumab cessation¹¹ was reported. Alping et al.¹⁴ reported, for the Swedish MS registry cohort, clinical deterioration in 18% of patients who switched from natalizumab to fingolimod, whereas B cell-depleting therapy with rituximab resulted in only 2% of patients with clinical deterioration within 1.5 years

Table 2 Baseline characteristics of patients who had a relapse/progression or were stable

	RRMS/aSPMS			PPMS		
	Relapse/progression (n = 19)	Stable (n = 86)	p Value	Relapse/progression (n = 2)	Stable (n = 29)	p Value
Female, n (%)	11 (58%)	52 (60%)		2 (100%)	12 (41%)	
Age at first ocrelizumab, y, mean ± SD	41.5 ± 9.5	38.5 ± 11.4	0.29	41.5 ± 2.1	50.2 ± 9.4	0.85
Disease duration, y, mean ± SD	7.4 ± 5.9	7.8 ± 6.8	0.82	5.0 ± 6.6	5.8 ± 6.2	0.86
EDSS score before ocrelizumab, mean ± SD; median (IQR; range)	4.1 ± 2.1; 5 (2–6; 0–7)	3.6 ± 1.8; 3 (2–5; 0–8)	0.24	4.5 ± 2.12; 4.5 (/; 3–6)	5.2 ± 1.6; 5 (4–6.5; 2.5–8.5)	0.53

Abbreviation: aSPMS = active secondary progressive MS; EDSS = Expanded Disability Status Scale; IQR = interquartile range; PPMS = primary progressive MS; RRMS = relapsing-remitting MS.

Table 3 Overview of side effects in 210 patients treated with ocrelizumab

	n = 210 patients
Side effects, n (%)	46 (22%)
Infusion-related side effects	19 (9%)
Headache	4
Tachycardia	3
Infusion reaction with erythema	4
Dyspnea	2
Vertigo/nausea	2
Pruritus	2
Pharynx edema	1
Syncope	1
Abdominal pain	1
Blurred vision for 30 min	1
Minor infections	17 (8%)
Upper respiratory infection	6
Urinary tract infection	5
Gastrointestinal infection	4
Herpes labialis	2
Fatigue/tiredness	10 (5%)
Hepatopathy	1
Others	3

Infusion-related side effects and mild infections were among the most frequent side effects. One case of drug-induced hepatopathy was documented. This was the only patient who had to temporarily discontinue therapy with ocrelizumab.

of observation. We observed only 2 patients who had relapses after switching from natalizumab to ocrelizumab (8%, 95% CI 0–19%), with the CIs indicating no difference compared with the Swedish cohort and significant lower relative numbers of recurrence of disease activity compared with the French cohort. As such, ocrelizumab following natalizumab, e.g., in patients at high risk of PML may be a promising option, with rather low risks of return of disease activity or severe adverse effects in the short term. As suggested already by the TOFINGO trial, our data furthermore corroborate the notion that washout time intervals during treatment switch should be as short as possible.¹⁷

Unexpectedly, the number of patients who displayed clinical progression following the switch from fingolimod to ocrelizumab was rather high (20%, 95% CI 0–43%). However, the CI indicates that this observation may have occurred by chance or sampling error, as based on only 3 individuals with reported EDSS progression, and no relapses during a short

observational period. Furthermore, the average EDSS score of these 3 patients was above 5 with disease duration longer than 8 years already at baseline, suggestive of a subgroup of patients with secondary progressive disease course where ocrelizumab might be less effective.

The overall ARR of all patients with RRMS/aSPMS of our cohort was 0.17 (95% CI 0.10–0.24), which is very similar to the ARR of the clinical phase 3 trial OPERA 1 (0.16, 95% CI 0.12–0.20), indicating that ocrelizumab seems to be as effective also under real-world conditions at least on the short run.

Limitations are that data were retrieved from chart review and discharge letters. This and the lack of imaging source data and site-specific differences in documenting and interpreting clinical symptoms may have influenced our results. Longer registry and postauthorization safety study data are needed to corroborate our first impressions of effectiveness and safety of ocrelizumab in the postmarketing setting. Most importantly, comparative studies that assess clinical effectiveness, safety, and patient-reported outcomes of different MS disease-modifying drugs, including the different B cell-depleting compounds, are highly warranted and partly underway, such as Combat-MS (NCT03193866).

Questions to be answered in the future concern the use of B-cell depletion in the long run in MS, individualized treatment regimens such as extended dosing intervals beyond year 2 or 3 of therapy, treatment holidays, or planned treatment cessations with wait-and-watch strategies. In particular, in patients in whom hypogammaglobulinemia or higher infection rates can be expected, such strategies may be unavoidable despite a risk of return of MS disease activity.

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Appendix Authors

Name	Location	Contribution
Erik Ellwardt, MD	Department of Neurology, Johannes Gutenberg University Mainz, Germany	Designed the study, collected data, performed data analysis, and wrote the manuscript
Leoni Rolfes, MD	Department of Neurology, University of Muenster, Germany	Collected data and wrote the manuscript
Julia Klein	Department of Neurology, University of Cologne, Germany	Collected data and wrote the manuscript

Appendix (continued)

Name	Location	Contribution
Katrin Pape, MD	Department of Neurology, Johannes Gutenberg University Mainz, Germany	Collected data and wrote the manuscript
Tobias Ruck, MD	Department of Neurology, University of Muenster, Germany	Collected data and wrote the manuscript
Heinz Wiendl, MD	Department of Neurology, University of Muenster, Germany	Collected data and wrote the manuscript
Sven G. Meuth, MD	Department of Neurology, University of Muenster, Germany	Collected data and wrote the manuscript
Frauke Zipp, MD	Department of Neurology, Johannes Gutenberg University Mainz, Germany	Collected data and wrote the manuscript
Michael Schroete, MDr	Department of Neurology, University of Cologne, Germany	Collected data and wrote the manuscript
Clemens Warnke, MD	Department of Neurology, University of Cologne, Germany	Collected data and wrote the manuscript
Stefan Bittner, MD	Department of Neurology, Johannes Gutenberg University Mainz, Germany	Designed the study and wrote the manuscript

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