Clinical Neurology and Neurosurgery 197 (2020) 106142

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Ocrelizumab Treatment in Patients with Primary Progressive Multiple Sclerosis: Short-term Safety Results from a Compassionate Use Programme in Germany

Sebastian Rauer [a,*], Muna-Miriam Hoshi [b], Refik Pul [c], Mathias Wahl [d], Matthias Schwab [e], Judith Haas [f], Gisa Ellrichmann [g], Markus Krumbholz [h], Björn Tackenberg [i,j], Kai-Uwe Saum [k], Fabian Buck [k], Jost Leemhuis [k], Anita Kretschmann [k], Orhan Aktas [l]

[a] Klinik für Neurologie und Neurophysiologie, Universitätsklinikum Freiburg, Freiburg, Germany
[b] Neurologische Klinik, Technische Universität München, Munich, Germany
[c] Klinik für Neurologie, Universitätsklinikum Essen, Essen, Germany
[d] Zentrum der Neurologie und Neurochirugie, Universitätsklinikum Frankfurt, Frankfurt, Germany
[e] Klinik für Neurologie, Universitätsklinikum Jena, Jena, Germany
[f] Jüdisches Krankenhaus Berlin, Berlin, Germany
[g] Klinik für Neurologie, St. Josef-Hospital, Bochum, Germany
[h] Department of Neurology & Stroke and Hertie-Institute for Clinical Brain Research, Eberhard Karl University of Tübingen, Tübingen, Germany
[i] Zentrum für Neuroimmunologie, Universitätsklinikum Marburg, Marburg, Germany
[j] F. Hoffmann-La Roche AG, Basel, Switzerland
[k] Roche Pharma AG, Grenzach-Wyhlen, Germany
[l] Klinik für Neurologie, Medizinische Fakultät, Universitätsklinikum Düsseldorf, Düsseldorf, Germany

ARTICLE INFO

Keywords:
Multiple sclerosis
Ocrelizumab
Disease-modifying therapy
Primary progressive multiple sclerosis
Compassionate use
Real-world data

ABSTRACT

Objectives: In January 2018, the European Union (EU) approved ocrelizumab in relapsing multiple sclerosis (RMS) and as the first disease-modifying therapy (DMT) for patients with primary progressive multiple sclerosis (PPMS) with efficacy proven in a phase 3 randomised controlled trial. Eleven months prior to the European regulatory approval, a compassionate use programme (CUP) made ocrelizumab available to 489 patients with PPMS in Germany, thereby for the first time providing a therapeutic option to patients with PPMS who could not participate in ocrelizumab studies. Here, we report real-world patient characteristics and short-term safety data of patients with PPMS treated with ocrelizumab in this CUP.

Patients and methods: This CUP was initiated in February 2017 – shortly before US Food and Drug administration approval in March 2017 – and ended in January 2018, following ocrelizumab approval in the EU. Adult patients (age ≥18 years) with PPMS who had a positive benefit/risk ratio according to the treating physician were eligible for inclusion at German treatment centres. The main exclusion criteria were current/recent treatment with other immune therapies and unresolved/chronic/active infections. Patients received methylprednisolone and an antihistamine before treatment with intravenous ocrelizumab in 6-month cycles. The first ocrelizumab dose was a 300 mg infusion followed by a second 300 mg infusion 2 weeks later; subsequent doses were delivered as a single 600 mg infusion. Adverse events were reported immediately.

Abbreviations: AE, adverse event; CTCAE, NCI Common Terminology Criteria for Adverse Events; CUP, compassionate use programme; EDSS, Expanded Disability Status Scale; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; IgG, immunoglobulin G; IRR, infusion-related reaction; IV, intravenous; JCV, John Cunningham virus; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; MRI, magnetic resonance imaging; MS, multiple sclerosis; NARCOMS, North American Research Committee on Multiple Sclerosis; PPMS, primary progressive MS; RCT, randomised controlled trial; RMS, relapsing MS; RRMS, relapsing-remitting MS; SAE, serious adverse event.

* Corresponding author at: Klinik für Neurologie und Neurophysiologie, Universitätsklinikum Freiburg, Breisacher Str. 64, 79106 Freiburg, Germany.
E-mail addresses: sebastian.rauer@uniklinik-freiburg.de (S. Rauer), muna.hoshi@ms-klinik.de (M.-M. Hoshi), refik.pul@uk-essen.de (R. Pul), wahl@med.uni-frankfurt.de (M. Wahl), matthias.schwab@med.uni-jena.de (M. Schwab), judith.haas@jkb-online.de (J. Haas), gisa.ellrichmann@rub.de (G. Ellrichmann), markus.krumbholz@uni-tuebingen.de (M. Krumbholz), tackenbb@staff.uni-marburg.de (B. Tackenberg), kai-uwe.saum@roche.com (K.-U. Saum), fabian.buck@roche.com (F. Buck), jost.leemhuis@roche.com (J. Leemhuis), anita.kretschmann@roche.com (A. Kretschmann), orhan.aktas@med.uni-duesseldorf.de (O. Aktas).

https://doi.org/10.1016/j.clineuro.2020.106142
Received 3 February 2020; Received in revised form 26 June 2020; Accepted 5 August 2020
Available online 12 August 2020

Results: Of 580 requests received from 104 centres, 525 patients met the eligibility criteria. Thirty-five patients did not participate due to withdrawal by the treating physician, and one due to death prior to treatment. A total of 489 patients received at least one 600 mg dose of ocrelizumab (administered as two 300 mg infusions) and 51 received a second dose. Due to termination of the CUP upon marketing authorisation, the maximum follow-up period was 12 months. Median patient age was 52 years (range: 24–73), and 49% were female. Previous immunomodulatory or immunosuppressive therapies had been received by 41% of patients, with the most commonly used being glucocorticoids, mitoxantrone, interferon-β and glatiramer acetate. Patients with a previous malignancy, serious disease or infection (42 patients, 9%) had recovered from this prior to the CUP. Nine serious adverse events and 70 non-serious adverse events were reported in 40 patients. Adverse event categories were generally consistent with the known safety profile of ocrelizumab; one patient had carry-over progressive multifocal leukoencephalopathy (PML) due to previous natalizumab treatment.
Conclusion: This CUP provides first real-world observations of ocrelizumab for the treatment of PPMS in a large patient cohort in Germany, supporting that ocrelizumab is generally well-tolerated in clinical practice. Physicians should be vigilant for early symptoms of PML, as to date, 9 PML cases that were all confounded have been reported in patients treated with ocrelizumab worldwide, with 8 carry-over cases from a prior DMT.

1. Introduction

Among 2.5 million people affected by multiple sclerosis (MS) worldwide Ehsan and Xixis, 2018, 15% are diagnosed with primary progressive MS (PPMS) [2]. PPMS is defined by gradual deterioration of neurological function, without distinct relapses and remissions [2]; symptoms slowly develop over months or years [13]. There is no curative treatment available for MS. Immunotherapies aim to slow disease progression and reduce the frequency and length of relapses by predominantly targeting inflammation. Despite the wide range of therapies for relapsing-remitting MS (RRMS), few substances have shown any promise in the treatment of PPMS, e.g. rituximab in certain subgroups [10]. Therefore, establishing clinically effective therapies for patients with PPMS is an urgent priority [9].

Prior to January 2018, no approved disease-modifying therapies for PPMS were available in the EU. Thus, the humanised anti-CD20 antibody ocrelizumab (Ocrevus®, F. Hoffmann-La Roche AG, Basel, Switzerland), is the first approved disease-modifying therapy for PPMS treatment, with US approval granted in March 2017 [19] and European approval in January 2018 [6]. Ocrelizumab specifically targets CD20-expressing cells and thus selectively and efficiently depletes B-lymphocytes.

The phase 3 ORATORIO trial evaluated the safety and efficacy of ocrelizumab in PPMS: Ocrelizumab significantly lowered the rate of clinical disability progression and magnetic resonance imaging (MRI) activity compared with placebo [15], without any significant differences in serious adverse events (SAEs) and serious infections. Further safety data are currently collected throughout the open-label ORATORIO trial extension phase.

Compassionate use programmes (CUPs) provide patients with serious or life-threatening conditions access to investigational drugs prior to regulatory approval [14], simultaneously generating valuable real-world safety data [3]. Prior to EU approval of ocrelizumab, the present CUP provided ocrelizumab to patients with PPMS who, according to their treating physician, would benefit from this innovative treatment option. We present patient characteristics and short-term safety outcomes.

2. Materials and Methods

This CUP was authorised by the Paul-Ehrlich-Institute as local regulatory authority and initiated in February 2017. All patients provided written informed consent prior to treatment. Participating physicians in German hospitals and medical practices were board-certified neurologists with experience in PPMS treatment and patient management.

2.1. Eligibility criteria

Patients were eligible for inclusion if they had been diagnosed with PPMS according to McDonald criteria 2010 [16], and were considered by the treating physician to have a positive benefit/risk ratio for treatment with ocrelizumab. For women and men of childbearing potential, agreement to use double-barrier contraception was required during treatment and for 6 months after the last dose. Exclusion criteria included current or recent treatment with another immunosuppressive/immunomodulatory therapy, hypersensitivity to ocrelizumab, chronic or active infections, severely immunocompromised state, and suspected or confirmed progressive multifocal leukoencephalopathy (PML) or other severe opportunistic infections in the patient's medical history. Patients eligible for any ongoing Roche-sponsored or investigator-initiated clinical trials of ocrelizumab were excluded, as were patients with any current/planned vaccinations within 6 weeks prior to initiation of ocrelizumab treatment. Pregnancy, breast feeding, anti-neoplastic treatment, and serious liver, kidney, lung or heart disease were also exclusion criteria.

2.2. Treatment plan

Patients who had received a previous immunotherapy were recommended to undergo a washout period before ocrelizumab treatment. These periods were recommended to last until remission of therapy-related effects (maximum change in blood count by grade 1, >500 $CD4^+$ T cells/mm^3) and at least 4 weeks for teriflunomide and fingolimod, 6 weeks for azathioprine, methotrexate, ciclosporine A, cyclophosphamide, mitoxantrone, laquinimod, and masitinib, 12 weeks for natalizumab and daclizumab, and 6 months for rituximab; for interferon-β, glatiramer acetate, and dimethyl fumarate, no minimal washout period was recommended. To determine the optimal washout period for individual patients, physicians were advised to balance the risk of returning MS activity with possible additive immunosuppressive effects. Prior to starting treatment, each patient's medical history was documented, and laboratory tests were recommended. Visits were planned at the discretion of the treating physician. Patients underwent physical examination on treatment days, and their disease was reassessed at each visit.

In order to reduce the frequency of infusion-related reactions (IRRs), methylprednisolone (100 mg) and an antihistamine were given to patients prior to ocrelizumab treatment. Some patients also received paracetamol. Ocrelizumab was administered as an intravenous (IV) infusion (600 mg in 500 mL) every 6 months. The first dose was split into two 300 mg infusions (each 250 mL) 2 weeks apart. Subsequent doses were delivered as a single 600 mg IV infusion every 6 months.

As long as the treating physician considered treatment a benefit to the patient, ocrelizumab was continued. Pre-defined discontinuation criteria included any medical condition that could jeopardise the patient's safety, non-compliance, pregnancy, patient request and unacceptable toxicity due to ocrelizumab treatment.

Table 1
Baseline characteristics of patients in the compassionate use programme.

Baseline characteristics	
Total number of patients treated with ocrelizumab, n	489
Sex, n (%)	
Female	242 (49.5)
Median age, years	52.0
Age range, years	(24.0 – 73.0)
Number of previous immunotherapies, n (%)	
0	290 (59.3)
1	151 (30.9)
2	35 (7.2)
3	8 (1.6)
4	3 (0.6)
5	2 (0.4)

2.3. Safety

Infusion was stopped immediately if a patient experienced severe pulmonary symptoms, or in cases of grade 4 IRRs. For grade 3 IRRs, the infusion was stopped and only restarted once all IRR symptoms had resolved. For grade 1–2 IRRs, the infusion rate was reduced by half for at least 30 minutes. Ocrelizumab treatment was delayed in patients who developed an active infection until the infection was resolved.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 were used to categorise adverse events (AEs). Treating physicians were required to report all serious AEs (SAEs), non-serious AEs of special interest and pregnancies within 1 working day. AEs of special interest included IRRs, hypersensitivity reactions, opportunistic and serious infections, respiratory tract infections, herpes infection, hepatitis B reactivation and overdose (exceeding the approved intravenous ocrelizumab dose). Other non-serious AEs were reported periodically. After termination of the programme, one follow-up patient check was carried out, and all centres were contacted to control for complete AE/SAE reporting.

2.4. Statistical analysis

Data were collected from medical records to describe patient characteristics at baseline and safety outcomes during the CUP, including sex, age, previous therapies (type of therapy, duration of therapy), severe previous diseases, malignancies or infections, planned vaccinations until 6 weeks prior to participation, and AEs/SAEs classified by system organ classes (e.g. infections and infestations, nervous system disorders).

The patient sample was analysed using standard descriptive methods. For continuous variables, the median and corresponding minimum and maximum values were reported. For categorical variables, the absolute and relative frequencies were reported. All analyses were conducted with SAS software, version 9.4 (Cary, NC, USA).

3. Results

3.1. Patient demographics and characteristics

This CUP was approved in February 2017 and was terminated in January 2018 following EU approval of ocrelizumab. Of 580 patients screened at 104 centres in Germany, 525 patients met the eligibility criteria. Prior to starting treatment, 35 patients were withdrawn by their physician and one patient died for unknown reasons. Overall, 489 patients completed the first 600 mg dose of ocrelizumab; 51 patients received a second dose. Almost half of the participating centres (47.9%) treated 1–2 patients. 95.7% of the centres had experience in the administration of infusions.

The median age of patients who received at least 1 cycle of ocrelizumab was 52 years, and similar numbers of female and male patients participated (Table 1). While 59.3% of patients had received no prior immunotherapy, 30.9% had received one prior therapy, with ≤10% of patients receiving ≥2 prior therapies (Table 1).

Table 2
Immunotherapies received prior to ocrelizumab treatment in compassionate use programme (N = 489).

Therapy*	Patients, n (%) N = 489	Age distribution, years Median (min–max)
Glucocorticoids	80 (16.4)	52.0 (29.0–65.0)
Mitoxantrone	40 (8.3)	52.0 (37.0–64.0)
Interferon-β	37 (7.6)	50.0 (25.0–65.0)
Glatiramer acetate	15 (3.1)	51.0 (43.0–62.0)
Dimethyl fumarate	14 (2.9)	48.0 (29.0–52.0)
Teriflunomide	14 (2.9)	46.5 (35.0–65.0)
Rituximab	12 (2.5)	46.0 (38.0–54.0)
Masitinib**	11 (2.3)	52.0 (32.0–68.0)
Fingolimod	9 (1.9)	47.0 (25.0–60.0)
Natalizumab	9 (1.9)	53.0 (29.0–65.0)
Azathioprine	8 (1.6)	52.0 (41.0–65.0)
Laquinimod**	6 (1.2)	53.0 (38.0–55.0)
Cyclophosphamide	4 (0.8)	56.5 (37.0–65.0)
Daclizumab	4 (0.8)	45.5 (29.0–50.0)

*As there were no approved disease-modifying immunotherapies for primary progressive multiple sclerosis available, these therapies were administered off-label or due to an initial incorrect diagnosis of RRMS. **study medication (blinded trials).

Table 3
Duration of treatment prior to the compassionate use programme with the most frequently used therapies (one previous therapy: n = 151, two previous therapies: n = 35).

Prior medical treatment(s)	Frequency, n*	Duration, months Mean (min–max)	
		First therapy	Second therapy
One previous therapy: 5 most frequent therapies			
Glucocorticoids	33	20 (0.03–103)	–
Interferon-β	25	43 (1.00–114)	–
Mitoxantrone	23	25 (1.00–48)	–
Dimethyl fumarate	8	22 (4.00–42)	–
Glatiramer acetate	7	41 (8.00–72)	–
Two previous therapies: 3 most frequent therapy sequences			
Interferon-β – mitoxantrone	6	48 (1–96)	25 (6–107)
Mitoxantrone – glucocorticoids	6	25 (10–41)	27 (0.17–82)
Interferon-β – teriflunomide	4	28 (4–86)	19 (1–38)

*Only patients with treatment duration data are displayed (n = 133).

The most common prior therapies were glucocorticoids (16.4%), mitoxantrone (8.3%) and interferon-β (7.6%; Table 2). Seventeen patients (3.5%) received previous masitinib or laquinimod as part of a blinded trial.

Overall, 133 patients had treatment duration data. Of the patients with a single prior therapy, those who received interferon-β tended to have a longer previous treatment duration (mean, 43 months) compared with those who received glucocorticoids (20 months) or mitoxantrone (25 months; Table 3). Regarding patients with two prior therapies, patients who were treated with interferon-β+mitoxantrone had a longer overall previous treatment duration (73 months) than with mitoxantrone + glucocorticoids or interferon-β+teriflunomide (52 and 47 months, respectively; Table 3).

3.2. Previous diseases, infections or malignancies, and vaccinations

Forty-two (8.6%) patients who received ≥1 ocrelizumab dose had 56 past instances of: malignancy (2.7%), cardiac disease (2.9%), infections

(acute: 1.8%; chronic: 0.4%) and other severe diseases (3.9%) in their medical histories, from which they had fully recovered before inclusion in this programme. The most common severe previous diseases were chronic ischaemic heart disease, severe urinary tract infection and malignant neoplasm of the kidney (for detailed incidences see **supplementary Table S1**).

One hundred and five patients (21.5%) had planned vaccinations >6 weeks prior to the start of ocrelizumab treatment, with the most common being tetanus, pertussis and diphtheria (Table 4).

3.3. Safety

During this programme, no AE with fatal outcome was reported. Seventy-nine AEs were reported in 40 patients, including 9 SAEs in 7 patients (Table 5):

One patient developed IRR-like symptoms within 24 h following the first infusion, and this event was considered related to ocrelizumab. The patient was subfebrile (37.9 °C) and experienced mild leukocytosis and tachycardia, which resulted in prolonged hospitalisation. Symptoms were regressive without any intervention. According to the reporting physician, the patient most likely experienced an IRR and tolerated the second infusion well.

One single case of PML in this programme was a carry-over case from previous treatment with natalizumab between 2013 and 2017 (final infusion February 13, 2017), and assessed by the physician who treated the PML as unrelated to ocrelizumab treatment. The female patient was positive for anti-John Cunningham virus (JCV)-antibodies in plasma/serum in 2013. MS symptoms progressed during natalizumab treatment. The patient was enrolled following an MRI which was interpreted as showing no signs of PML by the local radiologist. In March 2017, the anti-JCV antibody index was 4.11; no lumbar puncture and JCV-DNA-polymerase chain reaction (PCR) were performed. After the initial two ocrelizumab infusions in April 2017, the PML diagnosis was confirmed based on a brain MRI and the detection of JCV-DNA in cerebrospinal fluid in May 2017. The same patient developed aspiration pneumonia a few days later. In June 2017, a subsequent MRI showed a progression of PML with additional reconstitution inflammatory syndrome. During hospitalisation, the patient received mefloquine, mirtazapine and maraviroc. Her communication skills and motor function improved, and she was discharged for further outpatient care in September 2017. In April 2019, the patient showed ongoing disease progression (Expanded Disability Status Scale (EDSS) 9.5). It is not clear whether progression was caused by PML or MS.

One event of herpes zoster infection, which was assessed as related to ocrelizumab, required hospitalisation for treatment with intravenous aciclovir, but did not result in ocrelizumab treatment discontinuation.

One patient experienced lymphopenia with a lymphocyte count of 1000/μL 12 days after the first ocrelizumab administration. The second infusion was therefore postponed for one week. The lymphocyte level further decreased to 750/μL; no B- and T-lymphocyte counts were available. The treating physician assessed the medically significant event as related to ocrelizumab.

A female patient developed a non-bacterial urinary tract infection, which was reported without causality assessment by the treating physician and resolved without any treatment after two days.

Following hospitalisation due to progressive neurological disorder and left arm paresis 18 days after the first ocrelizumab dose, one patient experienced a massive pulmonary embolism. Therapy with ocrelizumab was stopped.

A patient with a history of extensive demyelinating disease and fampridine therapy was hospitalised due to a “seizure”. The treating physician assessed the causality of the event –probably a non-convulsive status epilepticus as the event resolved after one day of treatment with levetiracetam – as related to fampridine and unrelated to ocrelizumab.

Non-serious AEs were reported in 40 patients, and the most common categories were general disorders and administration site conditions (16 events; Table 5). The most common non-serious AEs by preferred term were fatigue (10 events), headache and urinary tract infection (4 events for both; **Table S2**).

Table 4
Planned vaccinations until 6 weeks prior to participation in the compassionate use programme (N = 489).

Vaccination	Patients, n (%) N = 489
Tetanus	19 (3.9)
Pertussis	14 (2.9)
Diphtheria	14 (2.9)
Pneumococcal	13 (2.7)
General: refresher/catch-up	11 (2.2)
Influenza	9 (1.8)
Polio	6 (1.2)
Measles	5 (1.0)
Hepatitis B	4 (0.8)
Tick-borne encephalitis	3 (0.6)
Mumps	3 (0.6)
Rubella	2 (0.4)
Varicella zoster virus	2 (0.4)

Table 5
Adverse events per system organ class: Non-serious adverse events (n = 40 patients out of N = 489) and serious adverse events (n = 7 patients out of N = 489).

System organ class	Total number of non-serious adverse events per system organ class	Total number of serious adverse events per system organ class
General disorders and administration site conditions	16	
Blood and lymphatic system disorders		1
Nervous system disorders	9	2
Investigations	8	
Gastrointestinal disorders	7	
Injury, poisoning and procedural complications	7	1
Musculoskeletal and connective tissue disorders	6	
Infections and infestations	5	2
Skin and subcutaneous tissue disorders	3	
Cardiac disorders	2	
Psychiatric disorders	2	
Immune system disorders	1	
Metabolism and nutrition disorders	1	
Renal and urinary disorders	1	1
Respiratory, thoracic and mediastinal disorders	1	2
Vascular disorders	1	
Total	**70**	**9**

4. Discussion

Ocrelizumab is currently the only approved immunotherapy for patients with PPMS which demonstrated superior efficacy compared with placebo in a phase 3 trial. The FDA authorised ocrelizumab in March 2017; European regulators granted approval in January 2018. This CUP expanded access to ocrelizumab for 489 patients with PPMS in Germany who were unable to participate in ocrelizumab clinical studies, thereby bridging a significant 11-month treatment gap. The patient characteristics and short-term safety outcomes are the first real-world observations of ocrelizumab treatment in a large patient cohort with PPMS in Germany.

Age and sex distribution of the patient population in this CUP were

characteristic of patients with PPMS. Interestingly, patients ranged from 24 to 73 years old, representing the remarkably wide age spectrum found in real-life clinical PPMS conditions. The median age of patients was higher than in the ORATORIO study (52.0 vs. 46.0 years) [15] and confirmed the unmet medical need in elderly patients with PPMS. Accordingly, a North American Research Committee on Multiple Sclerosis (NARCOMS) Registry survey with 632 patients with PPMS reported a median age of 64.3 ± 8.9 years [18]. PPMS does not have the same female predominance as RRMS [2]; accordingly, approximately half of the patients included in this CUP were female.

Although no immunotherapies approved for PPMS treatment were available at the time of the CUP, a substantial proportion of patients had prior treatment with ≥1 such therapy either due to an initial incorrect RRMS diagnosis or due to the high unmet medical need. Despite a lack of evidence for the efficacy of immunotherapies other than ocrelizumab, off-label treatment at the discretion of patients and physicians, based on individual applications for health insurance coverage, was common practice. Accordingly, a recent European Charcot Foundation survey found that active PPMS, represented by the presence of ≥1 spinal cord or brain gadolinium-enhancing lesion, would influence the decision to initiate an immunotherapy; 70% would treat active PPMS with an immunotherapy (not including ocrelizumab, which was not yet approved) [7]. Off-label treatments did not substantially improve short- to medium-term disability outcomes in PPMS in an international MSBase cohort study based on 195 disease-modifying immunotherapy-treated patients and 338 untreated patients [12]; the MSBase cohort included only 6 patients who received ocrelizumab. In the ORATORIO trial, where patients treated with B-cell-targeted therapy/other immunosuppressive medication were excluded, only 11.6% of patients had received a previous immunotherapy in the 2 years before trial entry [15].

In this CUP, AEs were reported in 8.2% of patients (79 events) and SAEs in 1.8% of patients (9 events). AE categories were similar to those seen in the ORATORIO study, but AE rates were considerably lower than those reported in the phase 3 randomised clinical trials (RCTs), possibly due to AE documentation conducted in a real-world setting and less stringent monitoring of patients than under RCT conditions. In the ORATORIO trial total AE incidences were 95.1% in the ocrelizumab arm vs. 90.0% in the control arm, and the respective SAE rates were 20.4% vs. 22.2% [15]. AE and SAE incidences similar to those observed in ORATORIO were reported in OPERA I and OPERA II, both RCTs assessing ocrelizumab in patients with RMS [8].

IRRs are known to be common during treatment with monoclonal antibodies, occurring in 30.9–39.9% of patients treated with ocrelizumab during RCTs [8]; [15]. In this CUP, one IRR, classified as serious, was reported, which resolved without intervention. It is important that treating physicians are aware of the risk of IRRs when using ocrelizumab.

In contrast to high incidences of infection observed in RCTs (56.6–71.4%) [8]; [15], only 7 events in the category “infections and infestations” were reported. In view of the wide age spectrum observed in our programme, it is especially important to consider the impact of immunosenescence in elderly patients, i.e. the aging-related gradual dysregulation of immune function, which may increase the risk of infections and malignancies that are associated with immunosuppressive and immunomodulatory therapies. Ongoing and future registry-based analyses could provide more information about the impact of immunosenescence on the risk/benefit ratio of ocrelizumab and other B-cell depleting disease-modifying therapies [1]. PML is a main safety concern of treatment with natalizumab and to a lesser degree with fingolimod and dimethyl fumarate, especially in patients with impaired immune function. A low risk of PML has been associated with anti-CD20 antibodies, with a significant number of cases observed during combination treatment with rituximab in other disease areas than MS [4]. Although a case of PML was documented during this CUP, PML was determined to be carried-over from prior natalizumab treatment. As of April 2020, >160,000 people have been treated with ocrelizumab for RMS or PPMS globally, of which >158,000 received ocrelizumab in the post-marketing setting. As of 31 January 2020, no unconfounded PML case with ocrelizumab has been observed, i.e. one or several other risk factors for PML were present; 8 confirmed cases of carry-over-PML in patients with RMS/PPMS treated with ocrelizumab due to previous immunotherapies (natalizumab, in one case fingolimod) and one case of non-carry-over-PML were reported [17]. The potential contribution of ocrelizumab treatment to the non-carry-over-PML case among other confounding factors, such as potential immunosenescence (age 78 years) and low absolute lymphocyte count prior to (≤grade 1, no subtypes available) and during (≤grade 2, low CD4+ and CD8+ counts) treatment with ocrelizumab, is difficult to quantify but cannot be ruled out. To avoid ocrelizumab treatment of patients with existing PML, we recommend screening for PML using lumbar puncture and JCV-PCR as well as MRI before the first ocrelizumab infusion. Although, to date, no cases have been reported as being caused by ocrelizumab treatment either during clinical trials or during real-world treatment [11], physicians should consider the risk associated with immunosenescence and be vigilant for early PML symptoms.

This CUP aimed to provide an effective therapy to patients with PPMS prior to the approval of ocrelizumab, while simultaneously collecting valuable information on ocrelizumab safety in a real-world setting from a substantial number of patients. Legal restrictions in Germany prevent such CUPs from collecting any effectiveness data as well as from adapting usual principles, measures or outcome parameters required or preferable in clinical trials. Thus, inherent limitations of our non-trial, CUP-based data collection include the absence of measures to control selection and treatment bias. Due to its termination upon marketing authorisation, approximately 90% of patients received only one treatment cycle, and there was no extended follow-up period (maximum follow-up was for 12 months). This limited our analysis to short-term safety data from the safety documentation process during the CUP.

5. Conclusion

This CUP provides first real-world safety data of a large patient cohort with PPMS treated with ocrelizumab in Germany, based on a short-term observation period of ≤12 months. Patient age and disease stage were more heterogeneous than in RCT populations. The observations of this CUP support that ocrelizumab is generally well-tolerated in the real-world clinical treatment setting: AE categories were consistent with the known safety profile, with considerably lower AE and SAE rates than in RCTs. Physicians should be vigilant for early symptoms of PML, as to date, 9 PML cases that were all confounded have been reported in patients treated with ocrelizumab worldwide, with 8 carry-over cases from a prior disease-modifying therapy. Overall, the data provide physicians with valuable clinical insights and may help inform future treatment decisions.

6. CRediT author statement

Five of the authors are Roche employees involved in study design and/or data collection (FB, AK, JL, BT), data analysis and interpretation (FB, AK, JL, K-US), as well as manuscript development (FB, AK, JL, K-US, BT).

Sebastian Rauer: Investigation, Writing - Review & Editing
Muna-Miriam Hoshi: Investigation, Writing - Review & Editing
Refik Pul: Investigation, Writing - Review & Editing
Mathias Wahl: Investigation, Writing - Review & Editing
Matthias Schwab: Investigation, Writing - Review & Editing
Judith Haas: Investigation, Writing - Review & Editing
Gisa Ellrichmann: Investigation, Writing - Review & Editing
Markus Krumbholz: Investigation, Writing - Review & Editing
Björn Tackenberg: Investigation, Writing - Review & Editing
Kai-Uwe Saum: Formal analysis, Writing - Review & Editing

Fabian Buck: Writing - Review & Editing
Jost Leemhuis: Writing - Review & Editing
Anita Kretschmann: Writing - Review & Editing
Orhan Aktas: Investigation, Writing - Review & Editing

Acknowledgements and funding

We thank all patients, their families, physicians and nurses who participated in this CUP.

Funding: This research was funded by Roche Pharma AG, Grenzach-Wyhlen, Germany. This CUP was designed, conducted and sponsored by Roche Pharma AG. Ocrelizumab was provided at no cost to the patients and paid for by Roche Pharma AG. Five of the authors are Roche employees involved in study design and/or data collection (FB, AK, JL, BT), data analysis and interpretation (FB, AK, JL, K-US), as well as manuscript development (FB, AK, JL, K-US, BT). Medical writing assistance was provided by Physicians World Europe GmbH (Mannheim, Germany), supported by Roche Pharma AG.

Conflicts of interest

All authors received support for their contribution to this CUP as well as medical writing support for publication of the data from Roche Pharma AG, Grenzach-Wyhlen, Germany.

SR: consulting and lecture fees, grant and research support from Bayer Vital GmbH, Biogen, Celgene, Merck Serono, Novartis, Sanofi-Aventis, Genzyme, Roche and Teva; founding executive board member of ravo Diagnostika GmbH Freiburg.

M-MH: travel grants and honararia from Bayer Healthcare, Merck Serono and Biogen.

RP: consulting fees from Biogen, Merck Serono, and Novartis, lecture fees from Biogen, Sanofi Genzyme, Merck Serono, Mylan, Novartis and Roche; research support from Novartis.

MW: honorary fees from Genzyme, Merck.

MS: grant support from Novartis, membership in advisory councils at Roche, Merck, Novartis, Biogen, Sanofi and speaker's bureau fees from Teva, Merck, Novartis, Biogen, Sanofi, Bayer; travel grants: Teva, Merck, Novartis, Biogen, Sanofi.

JH: compensation for advisory boards and lectures from Novartis, Merck, Bayer, Biogen, Hoffmann-La Roche, Teva, Sanofi Genzyme.

GE: travel grants and honoraria form Biogen, TEVA Pharma, Bayer Healthcare, Novartis, Sanofi Genzyme, Roche Pharma AG. Scientific grant support from Biogen, TEVA Pharma, and Novartis. Participation in multiple clinical trials, including ocrelizumab-related trials.

MK: grants, traveling support and personal fees from Bayer, Biogen, Celgene, Genzyme, Novartis, Merck, Roche, Teva; participation in multiple clinical trials, including ocrelizumab-related trials.

BT: employee of F. Hoffmann-La Roche AG; personal speaker honoraria and consultancy fees as a speaker and advisor from Alexion, Bayer Healthcare, Biogen, CSL Behring, GRIFOLS, Merck Serono, Novartis, Octapharma, Roche, Sanofi Genzyme, TEVA, UCB Pharma; his University received unrestricted research grants from Biogen, Novartis, TEVA, Bayer Healthcare, CSL Behring, GRIFOLS, Octapharma, Sanofi Genzyme, UCB Pharma.

K-US, FB, JL, AK are employees of Roche Pharma AG.

OA: honoraria for speaking/consultation and travel grants from Almirall, Bayer Healthcare, Biogen, Chugai, Medimmune/VielaBio, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva; research grants from Bayer Healthcare, Biogen, Novartis, Teva, all with approval by the Rector of the Heinrich Heine University.

Declaration of Competing Interest

All authors received support for their contribution to this CUP as well as medical writing support for publication of the data from Roche Pharma AG, Grenzach-Wyhlen, Germany.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clineuro.2020.106142.

References

[1] M. Ancau, A. Berthele, B. Hemmer, CD20 monoclonal antibodies for the treatment of multiple sclerosis: up-to-date, Expert Opin Biol Ther 19 (8) (2019) 829–843.
[2] J. Antel, S. Antel, Z. Caramanos, D.L. Arnold, T. Kuhlmann, Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? Acta Neuropathol 123 (5) (2012) 627–638.
[3] G. Balasubramanian, S. Morampudi, P. Chhabra, A. Gowda, B. Zomorodi, An overview of Compassionate Use Programs in the European Union member states, Intractable Rare Dis Res 5 (4) (2016) 244–254.
[4] K.R. Carson, A.M. Evens, E.A. Richey, T.M. Habermann, D. Focosi, J.F. Seymour, J. Laubach, S.D. Bawn, L.I. Gordon, J.N. Winter, R.R. Furman, J.M. Vose, A. D. Zelenetz, R. Mamtani, D.W. Raisch, G.W. Dorshimer, S.T. Rosen, K. Muro, N. R. Gottardi-Littell, R.L. Talley, O. Sartor, D. Green, E.O. Major, C.L. Bennett, Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project, Blood 113 (20) (2009) 4834–4840.
[6] EMA, Ocrevus: EPAR - Product Information, 2018. Accessed October 1, 2019. European Medicines Agency, https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf.
[7] O. Fernandez, M. Delvecchio, G. Edan, S. Fredrikson, G. Giovannoni, H.P. Hartung, E. Havrdova, L. Kappos, C. Pozzilli, P.S. Soerensen, B. Tackenberg, P. Vermersch, G. Comi, Survey of diagnostic and treatment practices for multiple sclerosis (MS) in Europe. Part 2: Progressive MS, paediatric MS, pregnancy and general management, Eur. J. Neurol. 25 (5) (2018) 739–746.
[8] S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.P. Hartung, B. Hemmer, F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee, J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura, S. Belachew, P. Chin, N. Mairon, H. Garren, L. Kappos, I. Opera, O.I.C. Investigators, Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis, N. Engl. J. Med. 376 (3) (2017) 221–234.
[9] H.P. Hartung, O. Aktas, Bleak prospects for primary progressive multiple sclerosis therapy: downs and downs, but a glimmer of hope, Ann. Neurol. 66 (4) (2009) 429–432.
[10] K. Hawker, P. O'Connor, M.S. Freedman, P.A. Calabresi, J. Antel, J. Simon, S. Hauser, E. Waubant, T. Vollmer, H. Panitch, J. Zhang, P. Chin, C.H. Smith, O. t. Group, Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial, Ann. Neurol. 66 (4) (2009) 460–471.
[11] A. Juanatey, L. Blanco-Garcia, N. Tellez, Ocrelizumab: its efficacy and safety in multiple sclerosis, Rev. Neurol. 66 (12) (2018) 423–433.
[12] J. Lorscheider, J. Kuhle, G. Izquierdo, A. Lugaresi, E. Havrdova, D. Horakova, R. Hupperts, P. Duquette, M. Girard, A. Prat, Anti-inflammatory disease-modifying treatment and disability progression in primary progressive multiple sclerosis: a cohort study, Eur J Neurol. (2018).
[13] D.H. Miller, S.M. Leary, Primary-progressive multiple sclerosis, Lancet Neurol 6 (10) (2007) 903–912.
[14] J.E. Miller, J.S. Ross, K.I. Moch, A.L. Caplan, Characterizing expanded access and compassionate use programs for experimental drugs, BMC Res Notes 10 (1) (2017) 350.
[15] X. Montalban, S.L. Hauser, L. Kappos, D.L. Arnold, A. Bar-Or, G. Comi, J. de Seze, G. Giovannoni, H.P. Hartung, B. Hemmer, F. Lublin, K.W. Rammohan, K. Selmaj, A. Traboulsee, A. Sauter, D. Masterman, P. Fontoura, S. Belachew, H. Garren, N. Mairon, P. Chin, J.S. Wolinsky, O.C. Investigators, Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis, N. Engl. J. Med. 376 (3) (2017) 209–220.
[16] C.H. Polman, S.C. Reingold, B. Banwell, M. Clanet, J.A. Cohen, M. Filippi, K. Fujihara, E. Havrdova, M. Hutchinson, L. Kappos, F.D. Lublin, X. Montalban, P. O'Connor, M. Sandberg-Wollheim, A.J. Thompson, E. Waubant, B. Weinshenker, J.S. Wolinsky, Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria, Ann. Neurol. 69 (2) (2011) 292–302.
[17] Roche, https://www. ocrelizumabinfo. global/en/homepage. html Accessed May 26, 2020. F, Hoffmann La -Roche Ltd. (2020).
[18] A. Salter, N.P. Thomas, T. Tyry, G.R. Cutter, R.A. Marrie, A contemporary profile of primary progressive multiple sclerosis participants from the NARCOMS Registry, Mult. Scler. 24 (7) (2018) 951–962.
[19] US-FDA, Ocrevus prescribing information, 2017. Accessed January 7, 2020. United States Food and Drug Administration, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761053s012lbl.pdf.