Ocrelizumab Compassionate Use Program for Patients with Primary Progressive Multiple Sclerosis in Germany

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INTRODUCTION

- Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by inflammation of the central nervous system,[1] and was estimated to affect nearly 250,000 people in Germany in 2015.[2]
- Approximately 15% of patients are diagnosed with primary progressive MS (PPMS), which features gradual worsening of neurological disability without relapses after symptom onset.[3]
- Ocrelizumab is a humanized anti-CD20 antibody (Ocrevus®, Roche Pharma AG), currently approved for the treatment of PPMS in Europe.[4]
- Safety and efficacy of ocrelizumab in patients with PPMS have previously been demonstrated in the phase III ORATORIO trial.[5]
- This German compassionate use program (CUP) was approved in February 2017 and terminated in January 2018, following the regulatory approval of ocrelizumab in Europe.

OBJECTIVE

- This CUP was initiated to provide ocrelizumab as a treatment option to patients with PPMS in Germany prior to regulatory approval in January 2018.

METHODS

Inclusion criteria

- Adult patients with a diagnosis of PPMS according to McDonald Criteria (2010).[6]
- Patients considered by the physician to have a potential positive benefit/risk ratio for treatment with ocrelizumab.
- Agreement to use an acceptable birth control method during the treatment period and for at least 6 months after the last dose.
- Signed informed consent.

Exclusion criteria

- Concomitant or recent use of other immunosuppressive or immunomodulatory therapies.
- Unresolved/chronic or active infection or severely immunocompromised state.
- Suspected/confirmed progressive multifocal leukoencephalopathy or other severe opportunistic infections in the patient's medical history.
- Actual/planned vaccination within 6 weeks prior to treatment initiation.
- Anti-neoplastic treatment for malignancies.
- Serious liver, kidney, lung or heart disease precluding ocrelizumab treatment.
- Pregnancy and breast-feeding.

Treatment plan

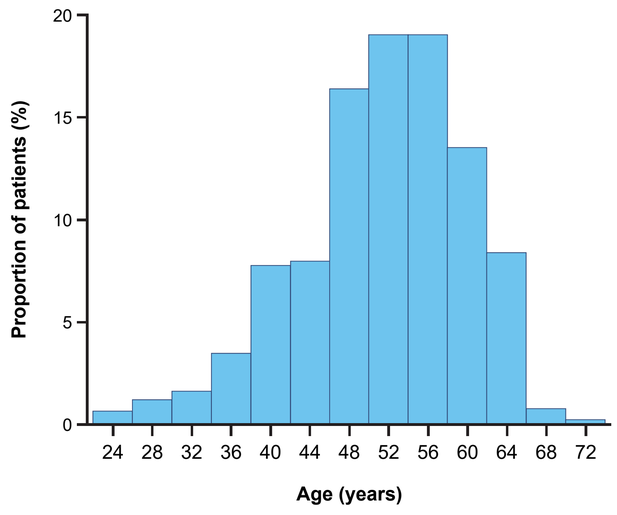
- Patients received 600 mg ocrelizumab as an intravenous infusion every 6 months for the duration of the CUP. The initial 600 mg dose was administered as two separate infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion.
- Methylprednisolone and antihistamines were administered prior to ocrelizumab to reduce the frequency of infusion-related reactions.
- After termination of the CUP no follow-up of the patients was performed.
- All adverse events (AEs) and serious AEs (SAEs) were recorded.

RESULTS

- Of 580 patients (104 centers), 525 fulfilled the inclusion criteria.
  - Thirty-five of these patients were withdrawn by the treating physician, and one patient did not receive treatment due to death.
- In total, 489 patients were treated with a first cycle of ocrelizumab and 51 patients received a second cycle.
- Two hundred and forty-seven patients were male (50.5%), 242 patients were female (49.5%).

Age distribution

Figure 1. Age distribution of ocrelizumab CUP patients



- Patient age ranged from 24–73 years (Figure 1). The median age of 52.0 years was higher than that of patients treated with ocrelizumab in the ORATORIO study (46.0 years).[5]

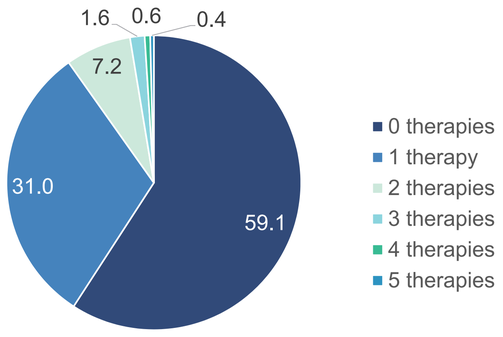
Previous therapies

- The majority of patients (n=288, 59.1%) had received no previous immunomodulatory or immunosuppressive therapy, followed by 151 (31.0%) patients who had received one previous therapy (Table 1, Figure 2).
- Patients who had previously received interferon beta and glatiramer acetate tended to remain on these therapies longer than patients receiving other therapies (Table 2).

Table 1. Previous therapies of CUP participants (N=489)

Previous therapies	Frequency n (%)	Age distribution (years) Median (Min – Max)
Glucocorticosteroids	80 (16.4)	52.0 (29.0 – 65.0)
Mitoxantrone	40 (8.3)	52.0 (37.0 – 64.0)
Interferon beta	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 (blinded study)	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 (blinded study)	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)

Figure 2. Number of previous therapies



Previous therapies per participant as a percentage of the total number of participants (N=489).

Table 2. Duration of previous therapy*

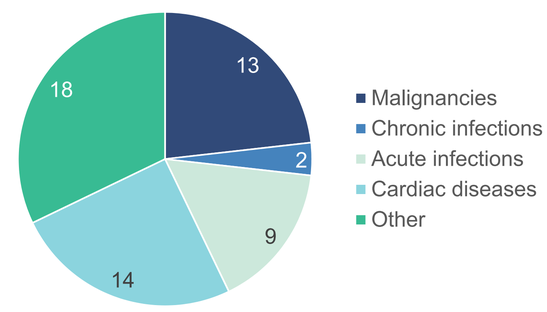
Previous therapy	Frequency n	Duration in months Mean	Min – Max
Cortisone	33	20	0.03 – 103
Interferon beta	25	43	1.00 – 114
Mitoxantrone	23	25	1.00 – 48
Dimethyl fumarate	8	22	4.00 – 42
Glatiramer acetate	7	41	8.00 – 72

*The most frequent 5 therapies used by patients who had one previous therapy.

Severe previous diseases, malignancies and infections

- Forty-two (8.6%) of 489 patients had a past malignancy, serious disease or infection in their medical history, but had fully recovered prior to inclusion in the ocrelizumab CUP (Figure 3).
- The most common malignancies/diseases/infections in the patients' medical history were chronic ischemic heart disease, urinary tract infection and malignant neoplasm of the kidney.

Figure 3. Severe previous diseases, malignancies and infections among ocrelizumab CUP participants



Incidences of severe previous diseases, malignancies and infections (n); 56 conditions in 42 patients were reported in total.

Planned vaccinations

Table 3. Planned vaccinations of CUP participants (N=489)

Planned vaccinations until 6 weeks prior to participation	Frequency n (%)
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)
FSME	3 (0.6)
Mumps	3 (0.6)
Rubella	2 (0.4)
Varicella zoster virus	2 (0.4)

SAFETY

Adverse events

- During the ocrelizumab CUP, 79 AEs were reported in 40 patients. Nine of these were classed as SAEs and were reported in 7 patients (Table 4).
  - The case of progressive multifocal leukoencephalopathy was a carry-over case from a previous treatment (natalizumab) and assessed as being unrelated to ocrelizumab treatment.

Table 4. Serious adverse events

System organ class	Total number of events in the system organ class	Events by preferred term
Blood and lymphatic system disorders	1	Lymphopenia
Infections and infestations	2	Herpes zoster Progressive multifocal leukoencephalopathy
Injury, poisoning and procedural complications	1	Infusion-related reaction
Nervous system disorders	2	Nervous system disorder Seizure
Renal and urinary disorders	1	Cystitis non-infective
Respiratory, thoracic and mediastinal disorders	2	Pneumonia aspiration Pulmonary embolism
Total Number of SAEs	**9**	

SAE, serious adverse event.

- Tables 5 and 6 show non-serious AEs by system organ class and preferred term, respectively. In total, 70 non-serious AEs were reported.
- Relatively few AEs and no fatal AEs were observed during the CUP, and the safety profile was consistent with ocrelizumab clinical trials.

Table 5. Non-serious adverse events per system organ class

System organ class	Total number of events in the system organ class
General disorders and administration site conditions	16
Nervous system disorders	9
Investigations	8
Gastrointestinal disorders	7
Injury, poisoning and procedural complications	7
Musculoskeletal and connective tissue disorders	6
Infections and infestations	5
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
Respiratory, thoracic and mediastinal disorders	1
Vascular disorders	1

Table 6. Non-serious adverse events that occurred in ≥2 events by preferred term*

Preferred term	Total number of events by preferred term
Fatigue	10
Headache	4
Urinary tract infection	4
Arthralgia	2
Dizziness	2
Gait disturbance	2
Pain in extremity	2
Pruritus	2
Tachycardia	2

*Not shown are intercepted medication error (3 events), no adverse event (3 events) and product preparation error (2 events).

DISCUSSION

- This CUP facilitated access to ocrelizumab treatment for 489 patients with PPMS in Germany up to 11 months prior to its regulatory approval in Europe.
- The age distribution in the CUP was characteristic for patients with PPMS.
- Although no approved therapies for PPMS were available at the time this CUP was conducted, 40.9% of patients received at least one previous immunomodulatory or immunosuppressive therapy.
- The adverse events reported during the CUP were consistent with the known safety profile of ocrelizumab; no new safety concerns were identified.
- The results from this CUP reflect real-world experience with ocrelizumab treatment, which may support future treatment decisions for patients with PPMS.

LITERATURE

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