ACAPELLA: Real-World Experience with Ocrelizumab, Nine-Year Data

Isabelle G. Messina M.S., Paola B. Castro Mendoza M.S., Ellen S. Lathi M.D., Andrew J. Bouley M.D., Joshua D. Katz M.D.
The Elliot Lewis Center for Multiple Sclerosis Care, Wellesley, MA

Background

Ocrelizumab (OCR) is a monoclonal antibody that targets CD20+ B-cells and is approved for treatment of relapsing (RMS) and primary progressive multiple sclerosis (PPMS). The pivotal phase II & III clinical trials excluded patients with advanced age and/or disability and preexisting conditions such as prior history of malignancy, prior immunosuppressive treatment, or low IgG[1,2]. Concerns have been raised about the potential for increased risk of infection, hypogammaglobulinemia, and malignancy with long-term use of OCR, particularly for older, more disabled patients.

The ACAPELLA trial is a long-term prospective observational study that includes those patients who would fall outside of the parameters specified in the clinical trials.The hypothesis in the ACAPELLA trial is that patients with higher levels of disability and/or advanced age would be at a higher risk for complications.

Objectives

We sought to evaluate the frequency of adverse events (AEs) in a real-world population of patients receiving OCR, including those with characteristics outside the inclusion parameters of the phase II & III trials, focusing on infections and malignancies.

Methods

ACAPELLA is a prospective, observational study which includes all consenting patients treated with commercial OCR at The Elliot Lewis Center since its release in March 2017. Cycle 1 includes two 300 mg doses of OCR, and Cycle 2 is the first full 600 mg dose. Baseline assessments include EDSS, brain MRI, and collection of medical history and laboratory data.

AEs were reported at the time of occurrence and/or assessed by questionnaire at the time of the patients' infusions. Infections were graded based on the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0[3].

Results

Table 1: Infections Per 100 Patient-Years (PY)

	Total Infections (2054 PY) N= 506	Age <55 (1472 PY) N=346	Age ≥ 55 (582 PY) N= 160	EDSS <6.0 (1657 PY) N=408	EDSS ≥ 6.0 (383 PY) N=98	Age ≥ 55 and EDSS ≥6.0 (205 PY) N=60	Combined Clinical Trial Data (5 Years)
Total Infections	75.9	79.8	66.0	78.8	66.1	59.5	76.2
Mild	22.4	25.4	14.9	25.2	11.2	12.2	
Moderate	51.0	52.3	47.8	51.8	49.6	43.4	
Severe	2.4	2.0	3.3	1.8	5.2	3.9	2
UTI	15.4	13.7	19.6	11.6	32.4	28.3	12.4
Recurrent UTIs	8.0	7.0	10.7	6.5	14.9	11.2	
URI	17.2	19.3	12.0	19.4	8.6	7.8	23.1
LRI	2.9	3.1	2.4	3.2	1.6	1.0	3.2
HSV-1 / HSV-2	7.3	7.9	5.7	8.1	3.9	6.8	0.3 (Combined HSV and Zoster)
Zoster	1.1	1.0	1.4	1.2	0.5	0.0	

CTCAE v5.0

Grade 1 Mild; asymptomatic or mild symptoms; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.

Table 2: Population Demographics

	Total Population	Relapsing	Progressive
	N=506	N=347	N=159
Total Patient Years	2054.1	1426.9	627.2
Mean Age	47	44	56
Female	378 (75%)	269 (78%)	109 (69%)
Mean EDSS	3.0	2.0	5.0
Mean Years Since Dx	20	20	19
IgG < LLN* at Baseline	16 (3%)	9 (3%)	7 (4%)

**LLN defined as < 600 mg/dL*

Table 3: Malignancies

SAE Malignancies	Age	EDSS	Cycles (#) (prior to diagnosis)	Prior IgG (mg/dL) (prior to diagnosis)
Breast (DCIS Grade II ER+/PR+)	60	2.5	3	955
Prostate (Stage T2b)	58	3.0	4	1020
Colon (Stage IIIb)	65	4.5	3	835
Colon (Stage IIIb)	42	2.0	2	1179
Melanoma of Shoulder (Stage I)	58	3.5	1	884
Colorectal (Stage IV)	57	6.0	2	1194
Head and Neck SCC	66	4.0	6	643
Neuroendocrine Small Bowel Tumor	44	4.0	6	962
Lentigo Maligna	62	3.0	9	1002
Melanoma of Back	61	3.5	9	495
Breast (Grade II ER+)	45	1.5	3	1186
Ductal carcinoma in situ	58	2.5	4	1123

- Patients with EDSS ≥ 6.0 had a rate of UTIs that was 32.4 per 100PY compared to 11.6 per 100PY in patients with EDSS < 6.0.
- Patients with EDSS ≥ 6.0 had a rate of URIs of 8.6 per 100PY compared to 19.4 per 100PY in those with EDSS < 6.0.
- Patients with EDSS ≥ 6.0 had a severe infection rate of 5.2 per 100PY, and those with age ≥ 55 had rate of 3.3 per 100PY. This is compared to rates of 1.8 and 2.0 in patients EDSS < 6.0 and age < 55, respectively.
- 15 patients (3%) had disease breakthrough with clinical relapse and/or new MRI activity, similar to the rate observed in the clinical trials.
- Malignancies occurred at a rate of 0.68 per 100PY; breast cancers occurred at a rate of 0.15 per 100PY.

Conclusions

Infections

- Patients with EDSS ≥ 6.0 had a higher risk of UTIs, which is not unusual in this population. There was no increased risk of non-severe infections with increased age or disability level.
- Interestingly, patients who were younger and/or had lower EDSS had higher rates of LRIs and URIs than patients who were older and/or had higher EDSS.
- Older and more disabled patients had a higher risk for severe infections.

Malignancies

- The breast cancer rate of 0.15 per 100 PY is similar to that observed in the SEER database (2020) of 0.15 per 100 PY[4], and the rate of 0.17 per 100PY in the combined OCR-studied populations.[5,6]

References:

1. Montalban X, Hauser SL, Kappos L et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. New England Journal of Medicine, 2017; 376:209-220
2. Hauser SL, Bar-Or A, Comi G et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. New England Journal of Medicine, 2017; 376:221-234
3. "Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0." National Cancer Institute. Published November 27, 2017. Accessed May 9, 2024. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.
4. SEER Incidence Data, November 2022 Submission (1975-2020), SEER 22 registries
5. Hauser SL, et al. ePoster presented at 39th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 11-13, 2023; Digital Congress. Presentation P304
6. Hauser SL, et al. ePoster presented at 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); September 18-20, 2024; Digital Congress. Presentation P300