ACAPELLA: Real-World Experience with Ocrelizumab Year Six Data

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Background

Ocrelizumab (OCR) is a humanized, 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]. The ACAPELLA trial is a prospective observational study that includes those patients who would fall outside of the parameters specified in the clinical trials.

In addition to adverse events (AEs), ACAPELLA sub-studies are evaluating the impact of OCR on immunoglobulin levels. Interim data analyses occur on a biyearly basis and findings will be reported annually.

Objectives

We sought to evaluate the frequency of 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

This is a prospective, observational study which includes all consenting subjects treated with commercial OCR at The Elliot Lewis Center since its release in March 2017. Baseline assessments include EDSS, brain MRI, collection of medical history including prior serious or recurrent infections, history of malignancy, history of immunosuppressive treatment, and laboratory data.

AEs were reported at the time of occurrence and assessed by questionnaire at the time of the subjects' infusions. Immunoglobulin levels were drawn just prior to infusion and repeated every 6 months. EDSS assessments were repeated yearly.

Results

Figure 1: Population by OCR Cycle

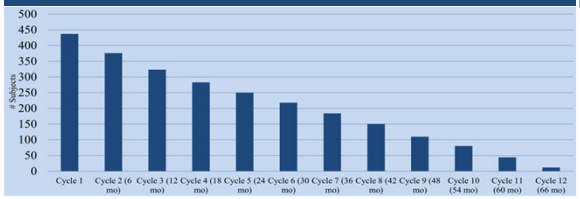

Table 1: Population Demographics

	Total Population	Relapsing	Progressive
	N=437	N=299	N=138
Mean Age	47	43	55
Female	74%	77%	65%
Mean EDSS	3.0	2.5	5.0
Mean Years Since Dx	15	13	18
Hx Immunosuppressive Tx	38 (9%)	20 (7%)	18 (13%)
IgG < LLN* at Baseline	15 (3%)	10 (3%)	5 (4%)

**LLN defined as < 600 mg/dL*

Table 3: Malignancies

SAE Malignancies	Age	EDSS	Mo. Since Last Dose	Cycles (#)	Prior IgG (mg/dL)
Breast (DCIS Grade II ER+/PR+)	61	2.5	4	3	955
Prostate (Stage T2b)	60	3.0	3	4	1020
Colon (Stage IIIb)	65	4.5	1	3	835
Colon (Stage IIIb)	42	2.0	4	2	1179
Colorectal (Stage IV)	57	6.0	11	2	1194
Head and Neck SCC	66	4.0	3	6	643
Neuroendocrine Small Bowel Tumor	44	4.0	4	6	962
Breast (Grade II ER+)	45	1.5	4	3	1186

Results Summary

- EDSS ≥ 6 was associated with a higher risk of UTI, otherwise there was no increase in AEs in patients with EDSS ≥ 6 and/or age ≥ 55.
- 12 patients (3%) had disease breakthrough with clinical relapse and/or new MRI activity, similar to the rate observed in the clinical trials.

Table 2: Infections per 100 Patient-Years (PY)

	Total Infections (1342.69 PY) N=437	Age <55 (881.73 PY) N=302	Age ≥ 55 (460.97 PY) N=135	EDSS <6.0 (1029.2 PY) N=348	EDSS ≥ 6.0 (313.49 PY) N=89	Age ≥ 55 and EDSS ≥ 6.0 (188.36 PY) N=52	Combined Clinical Trial Data (5 years)*
Total Infections w/o COVID-19	47.0	49.0	43.2	47.2	46.3	38.8	76.2
Mild	8.0	8.5	6.9	8.7	5.4	6.9	
Moderate	37.8	39.5	34.7	37.6	38.6	30.8	
Serious Infections	1.5	1.0	2.4	0.9	2.2	3.7	2.0
UTI	15.0	14.3	16.3	11.3	27.1	22.8	12.4
Recurrent UTI	7.7	7.0	9.1	6.4	12.1	10.1	
URI	15.6	15.3	16.1	15.3	16.6	7.4	23.1
LRI	2.1	2.3	1.7	2.4	1.0	1.1	3.2
HSV-1 / HSV-2	5.7	6.1	5.0	6.4	3.5	5.3	Combined HSV/Zoster infections 0.27
Zoster	0.8	0.8	0.9	1.0	0.3	0.0	
COVID-19 Infections	16.9	20.3	10.4	20.4	5.4	4.8	
Outpatient	16.0	19.1	10.2	19.7	3.8	4.2	
Hospitalized	0.7	0.5	1.3	0.7	1.0	0.5	
ICU/Death	0.1	0.1	0.2	0.1	0.3	0.0	

Conclusions

In patients treated with OCR, concerns have been raised about the potential for increased risk of infection, hypogammaglobulinemia, and malignancy with long-term use. The hypothesis in the ACAPELLA trial was that patients with higher levels of disability and/or older age may be at a higher risk.

Infections

- Patients with an EDSS ≥ 6.0 had a higher rate of UTIs, which is expected in this population. Otherwise, there was no clear increased risk of infections with either age ≥ 55 and/or disability level ≥ 6.
- There was no increase in the incidence of HSV or zoster in older and/or more disabled patients.
- 23 patients (5%) had serious non-COVID infections (requiring hospitalization) with no definitive correlation to age or disability level.
- 10 patients (2%) were hospitalized with COVID-19, 2 of whom died.

Malignancy

In our study, malignancies occurred at a rate of 0.59 per 100 PY; breast cancers occurred at a rate of 0.15 which is similar to that observed in the SEER database[3] and the combined OCR-studied populations[4-5].

References
1.Montalban X, Hauser SL, Kappos L et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. New England Journal of Medicine, 2017 Jan 19; 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 Jan 19; 376: 221-234
3.SEER Incidence Data, November 2022 Submission (1975-2020), SEER 22 registries
4.Hauser SL, et al. ePoster presented at 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 13-15, 2021; Digital Congress. Presentation P724
5.Hauser SL, et al. ePoster presented at 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 13-15, 2021; Digital Congress. Presentation P326