ACAPELLA: Real-World Experience with Ocrelizumab, 5-Year 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 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 the parameters specified in the clinical trials.

In addition to adverse events (AEs), ACAPELLA sub-studies assess the impact of OCR on immunoglobulin levels, CD19 reconstitution, and JCV antibody titers. Interim data analyses occur on a biyearly basis and findings are 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, mammograms (standard of care), collection of medical history including prior serious or recurrent infections, history of malignancy, history of immunosuppressive treatment, immunoglobulin levels, CD19 count, and JCV antibody with index.

AEs were assessed by questionnaire, patient interview and chart review. Immunoglobulin levels (LLN = 600mg/dL), CD19 count, and JCV antibody with index were drawn immediately prior to infusion and repeated at every infusion of OCR. EDSS assessments were repeated yearly.

Results

Figure 1: Population by OCR Cycle

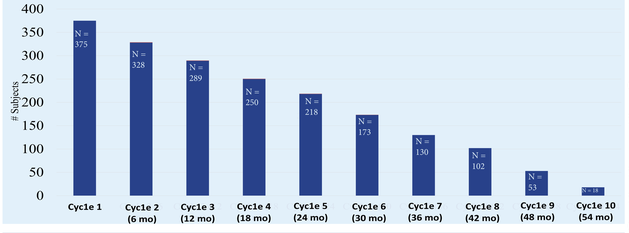

Table 1: Population Demographics

	Total Population	Relapsing	Progressive
	N = 375	n = 245	n = 130
Mean Age	48	43	56
Female	73%	76%	66%
Mean EDSS	3.5	2.5	5.0
Mean Years Since Dx	14	12	17
Hx Immunosuppressive Tx	36 (10%)	18 (7%)	18 (14%)
IgG Available at Baseline	358 (95%)	237 (96%)	121 (93%)
IgG < LLN at Baseline	15 (4%)	10 (4%)	5 (4%)

Table 3: Malignancies

SAE	Age	EDSS	Mo. Since Last Dose	Cycles (#)	Prior IgG (mg/dL)
Malignancies					
Grade II ER+/PR+ DCIS	61	2.5	4	3	955
Stage T2b Adenocarcinoma of Prostate	60	3.0	3	4	1020
Stage IIIb Colon Cancer	65	4.5	1	3	835
Stage IIIb Colon Cancer	42	2.0	4	2	1179
Colorectal Cancer Met to Liver	57	6.0	11	2	1194
Squamous Cell Carcinoma of neck	66	4.0	3	6	643

Results Summary

- EDSS ≥ 6 had a higher incidence of UTI, otherwise there was no increase in AEs in patients with EDSS ≥ 6 and/or age ≥ 55.

Table 2: Rates per 100 Patient-Years of Infections in the ACAPELLA Trial

	Total Infections (999.38 PY)	Age < 55 (n = 151; 639.90 PY)	Age ≥ 55 (n = 85; 359.48 PY)	EDSS < 6 (n = 176; 750.78 PY)	EDSS ≥ 6 (n = 60; 248.60 PY)	Age ≥ 55 and EDSS ≥ 6 (n = 37; 150.64 PY)	Combined Clinical Trial Data (5 years)[3]
Total Infections excluding COVID-19	49.4	52.8	43.4	49.8	48.3	40.5	76.2
Mild	8.1	9.4	5.8	8.9	5.6	6.0	---
Moderate	39.7	42.0	35.6	39.3	41.0	32.5	---
Serious	1.6	1.4	1.9	1.6	1.6	1.3	2.01
UTI	16.2	15.6	17.2	11.9	29.4	25.2	12.4
Recurrent UTI	5.9	5.6	6.4	4.1	11.3	7.3	---
URI	15.4	18.1	10.6	18.0	7.6	6.6	23.1
LRI	2.0	2.2	1.7	2.4	0.8	1.3	3.2
Total Herpes Virus Related Infections	6.4	6.9	5.5	7.6	2.8	4.6	0.27
HSV-1 / HSV-2	5.3	5.6	4.7	6.1	2.8	4.6	---
Zoster	1.1	1.3	0.8	1.5	0.0	0.0	---
COVID-19 Infections	8.9	11.1	5.0	10.8	3.2	2.0	---
Mild	7.2	9.1	3.9	8.9	2.0	1.3	---
Moderate	1.0	1.3	0.6	1.3	0.0	0.0	--
Severe	0.7	0.8	0.6	0.5	1.2	0.7	---
			0.6	0.5	1.2	0.7	

Conclusions

In the pivotal clinical trials, OCR had a low incidence of serious adverse events.[3] Concerns have been raised about the potential for increased risk of infection, hypogammaglobulinemia, and malignancy with long-term use. We hypothesize that patients with higher levels of disability and/or older age might be at a higher risk.

Infections

- Patients with an EDSS ≥ 6.0 had a slightly higher rate of UTIs, which is expected in this population.
- Otherwise, there was no increased incidence of infections in either older and/or more disabled patients.
- There was no increase in the incidence of HSV or zoster in older and/or more disabled patients.
- 22 patients (6%) had serious non-COVID infections (requiring hospitalization) with no correlation to age or disability level.

- 7 patients (2%) were hospitalized with COVID-19, 2 of whom died.

Malignancy

In our study, malignancies occurred at a rate similar to that observed in the general MS population[4].

Breakthrough Disease

- 11 patients (3%) had disease breakthrough with clinical relapse and/or new MRI activity, similar to the rate observed in the clinical trials.

Summary

With the exception of UTIs, which were more prevalent in patients with an EDSS > 6, we did not observe a higher rate of AEs in older and/or more disabled patients.

References
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