ACAPELLA: Real-World Experience with Ocrelizumab, Year Four 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, CD19 reconstitution, and JCV antibody titers. 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 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 reported at the time of occurrence and assessed by questionnaire at the time of the subjects' infusions. Immunoglobulin levels, CD19 count, and JCV antibody with index were drawn just prior to infusion and repeated every 6 months. EDSS assessments were repeated yearly.

Results

Figure 1: Population by OCR Cycle

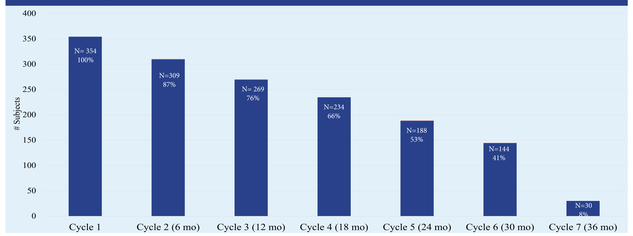

Table 1: Population Demographics

	Total Population	Relapsing	Progressive
	N = 354	n = 227	n = 127
Mean Age	48	44	56
Female	71%	74%	65%
Mean EDSS	3.5	2.5	5.0
Mean Years Since Dx	13	12	16
Hx Immunosuppressive Tx	33 (9%)	16 (7%)	17 (13%)
IgG Available at Baseline	337 (95%)	219 (97%)	118 (93%)
IgG < LLN⁕ at Baseline	14 (4%)	9 (4%)	5 (4%)

⁕ <600 mg/dL: local laboratory range LLN decreased from 694 mg/dL

Table 2: AE Occurrence

	Total Population (N = 354)	EDSS 0 - 3.5 (n = 224)	EDSS 4 - 5.5 (n = 48)	EDSS ≥ 6 (n = 82)	Age < 55 (n = 220)	Age ≥ 55 (n = 134)	Age ≥ 55 and EDSS ≥ 6 (n = 48)
Disease Breakthrough	12 (3%)	7 (3%)	1 (2%)	4 (5%)	9 (4%)	3 (2%)	2 (4%)
Clinical Relapse w/ MRI Activity	6 (2%)	5 (2%)	-----	1 (1%)	6 (3%)	-----	-----
Clinical Relapse w/o MRI Activity	3 (<1%)	1 (<1%)	-----	2 (2%)	1 (<1%)	2 (1%)	2 (4%)
MRI Relapse w/o Clinical Activity	3 (<1%)	1 (<1%)	1 (2%)	1 (1%)	2 (1%)	1 (1%)	-----
Subjects with ≥ 1 Moderate Infection Requiring Antibiotics	126 (36%)	72 (32%)	17 (35%)	37 (45%)	77 (35%)	49 (37%)	21 (44%)
≥ 1 URI	57 (16%)	42 (19%)	5 (12%)	6 (8%)	43 (20%)	14 (10%)	3 (6%)
≥ 1 LRI	11 (3%)	10 (4%)	-----	-----	9 (4%)	2 (1%)	1 (2%)
≥ 1 UTI ♦	66 (19%)	25 (11%)	3 (7%)	23 (30%)	34 (15%)	32 (24%)	20 (42%)
≥ 1 Other Infection ♦♦	43 (12%)	27 (12%)	8 (17%)	8 (10%)	30 (14%)	13 (10%)	2 (4%)
Serious Infections*	17 (5%)	11 (5%)	2 (4%)	6 (7%)	12 (5%)	8 (2%)	3 (6%)
HSV-1 / HSV-2	28 (8%)	18 (8%)	6 (13%)	4 (5%)	19 (9%)	9 (7%)	4 (8%)
Zoster	9 (3%)	7 (3%)	2 (4%)	-----	6 (3%)	3 (2%)	-----
Benign Neoplasms▫	11 (3%)	8 (4%)	-----	3 (4%)	6 (3%)	2 (2%)	1 (2%)
COVID-19 Infections **	20 (6%)	13 (6%)	3 (6%)	4 (5%)	14 (6%)	6 (4%)	3 (6%)

♦ 23 of these subjects reported a history of ≥ 1 UTI/year ♦♦ Including mastitis, cellulitis (5), dental abscess (3), impetigo, fungal vaginitis (2), otitis (6), conjunctivitis (2), strep pharyngitis (2), cutaneous abscess (4), stye, prostatitis.

▫ Benign neoplasms: breast papilloma (2), breast fibroadenoma, ovarian serous cystadenoma, adrenal adenoma, vulvar intraepithelial neoplasia, cervical hyperplasia, gastric polyp (2).

** 13 cases were mild and resolved without intervention, 1 case was moderate and required treatment, and 6 cases were severe requiring hospitalization.

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 was associated with a higher risk of UTI, otherwise there was no increase in AEs in patients with EDSS ≥ 6 and/or age ≥ 55.
- Six patients developed malignancies of different types (see Table 3).

Conclusions

OCR and other anti-CD20 antibodies generally have an excellent safety profile. 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 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.
- 17 patients (5%) had serious infections requiring hospitalization with no correlation to age or disability level.

Malignancy

In our study, malignancies occurred at a rate similar to that observed in the general MS population[3].

Breakthrough Disease

- 12 patients (3%) had disease breakthrough with clinical relapse and/or new MRI activity, similar to the rate observed in the clinical trials.
- 22 (6%) had mild to moderate post-infusion symptoms and/or prolonged malaise, but this was not associated with early B-cell reconstitution.

Although our hypothesis was that older and/or more disabled patients might have higher rates of AEs. Thus far in our cohort of 354 patients treated with OCR for up to 4 years, this was not observed.

References
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3. Marrie MA, Reider N, Cohen J, et al. A Systematic Review of the Incidence and Prevalence of Cancer in Multiple Sclerosis, Multiple Sclerosis Journal, 2015 Mar; 21(3):294-304