Real-World Experience with Ocrelizumab, 8-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 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

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. 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 subjects' 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 Population N=499 (1851.6 PY)	Age < 55 N=343 (1319.5 PY)	Age ≥ 55 N=156 (532.1 PY)	EDSS < 6.0 N=402 (1486.5 PY)	EDSS ≥ 6.0 N=97 (354.9 PY)	Age ≥ 55 and EDSS ≥ 6.0 N=59 (191.2 PY)	Combined Clinical Trial Data (5 Years)
Total Infections	77.2	80.8	68.4	80.7	65.1	58.0	76.2
Mild	22.0	24.9	14.8	25.0	10.1	11.0	
Moderate	52.8	54.0	50.0	53.9	49.9	42.9	
Severe	2.5	2.1	3.6	2.0	5.1	4.2	2.0
UTI	16.0	14.5	19.9	12.6	31.0	26.7	12.4
Recurrent UTIs	8.6	7.4	11.7	7.1	14.9	12.0	
URI	15.9	17.7	11.5	18.0	7.9	7.3	23.1
LRI	2.9	3.0	2.6	3.2	1.7	1.0	3.2
HSV-1 / HSV-2	7.5	8.0	6.2	8.3	4.2	7.3	Combined HSV/Zoster infections
Zoster	1.1	1.0	1.5	1.3	0.6	0.0	0.3

***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.

Figure 1: Population by OCR Cycle

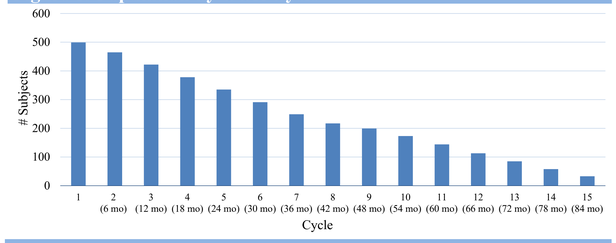

Table 3: Population Demographics

	Total Population	Relapsing	Progressive
	N=499	N=343	N=156
Total Patient Years	1851.64	1266.6	585.1
Mean Age	47	44	56
Female	374 (75%)	267 (78%)	107 (69%)
Mean EDSS	3.0	2.5	5.0
Mean Years Since Dx	20	20	19
Hx Immunosuppressive Tx	40 (8%)	21 (6%)	19 (12%)
IgG < LLN* at Baseline	15 (3%)	9 (3%)	6 (4%)

**LLN defined as < 600 mg/dL*

Table 2: 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

Results Summary

- Patients with EDSS ≥ 6.0 had a rate of UTIs that was 31.0 per 100PY compared to 12.6 per 100PY in patients with EDSS < 6.0.
- Patients with EDSS ≥ 6.0 had a rate of URIs of 7.9 per 100PY compared to 18.0 per 100PY in those with EDSS < 6.0.
- Patients with EDSS ≥ 6.0 had a severe infection rate of 5.1 per 100PY, and those with age ≥ 55 had rate of 3.6 per 100PY. This is compared to rates of 2.1 and 2.0 in patients age < 55, and EDSS < 6.0, respectively.
- 14 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 0.76 per 100PY; breast cancers occurred at a rate of 0.16 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.
- 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, possibly because the latter took more precautions to avoid infection.
- Older and more disabled patients had a higher risk for severe infections.

Malignancies

The breast cancer rate of 0.16 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:

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