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

An Observational Study Evaluating Safety in Patients with Relapsing and Progressive Multiple Sclerosis: No News is Good News

Hannah M. Geils[1], Joshua D. Katz[1], Ellen S. Lathi[1], India C. Stribling[1]
[1]The Elliot Lewis Center for Multiple Sclerosis Care, Wellesley, MA

Background

Ocrelizumab (OCR) is a humanized monoclonal antibody targeting CD20+ B-cells and is FDA approved for treatment of relapsing remitting multiple sclerosis (RRMS) 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, and low IgG. The ACAPELLA trial is a prospective observational safety 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 are evaluating the impact of OCR on JCV antibody titers, immunoglobulin levels, CD19 reconstitution, and malignancy occurrence and outcomes in patients with and without a prior history of cancer. Interim data analyses occur on a biyearly basis and findings will be reported annually.

Objectives

We sought to examine the frequency of AEs in a real-world population receiving OCR with characteristics outside the inclusion parameters of the phase II & III trials, focusing on infections requiring antibiotics and neoplasms. This dataset reflects results two years after FDA approval of OCR.

Methods

This study includes all 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, JCV antibody with index, and CD19 count.

AEs and concomitant medications were reported by patients at the time of occurrence and assessed by questionnaire at the time of their infusions. Immunoglobulin levels, JCV antibody with index, and CD19 count are repeated every 6 months prior to infusion. EDSS assessments are repeated yearly.

Results

- No difference was observed in AEs or infusion related reactions (IRRs) between the RRMS and progressive MS population. IRRs did not correlate with B-cell reconstitution.
- None of the subjects with preexisting history of neoplasm had recurrence: 2 pituitary adenomas, 2 meningiomas, 8 breast cancers, 3 thyroid cancers, 2 Non-Hodgkin's lymphomas, 2 prostate cancers, and 5 squamous cell carcinomas (basal cell excluded).
- 2 pregnancies: one (age 37) ectopic pregnancy occurred 7 months after last OCR dose. One (age 43) occurred ~2 weeks after the last OCR dose, resulting in spontaneous abortion at 3 months.
- 10 subjects had at least one low IgG value after treatment with OCR.
- 18 subjects (7%) reported notable, short-lived symptoms 1-7 days following OCR treatment: rash, headache, dyspnea, nausea, and arthralgias/myalgias.

Figure 1: Population by OCR Cycle

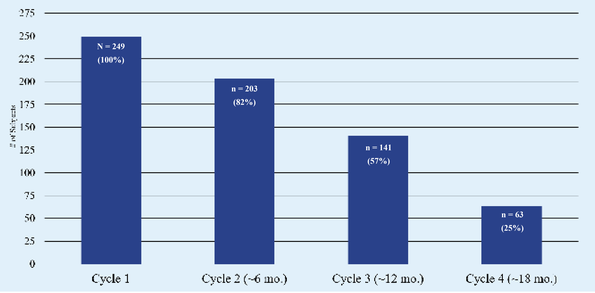

Table 1: Population Demographics

	Total Population	Relapsing	Progressive
Subjects	N = 249	n = 154	n = 95
Mean Age	49	45	56
Female	71%	74%	65%
Mean EDSS	3.6	2.7	5.1
Mean Years Since Dx	13	11	15
Hx Immunosuppressive Tx	26 (10%)	12 (8%)	14 (15%)
Igs Available at Baseline	235 (94%)	147 (95%)	88 (93%)
IgG < LLN⁕ at Baseline	23 (9%)	16 (11%)	7 (8%)

⁕ <694 mg/dL

Table 3: SAE Occurrence (Requiring Hospitalization)

SAE	Age	EDSS	Time Since Last OCR Dose (mo)	Cycles (#)
Laryngopharyngitis	64	3.0	1	2
Mandibular Abscess (MRSA)	50	6.0	6	1
Mycoplasma PNA/Aseptic Meningitis	52	2.5	3	1
Diverticulitis	51	2.0	1	1
Abdominal Wall Abscess	60	2.5	4	1
Appendicitis	43	2.5	2	3
Aspiration Pneumonia	53	7.0	<1	2
Stage IIIb Colon Cancer	65	4.5	1	3

Table 2: AE Occurrence

	Total Population (N = 249)	EDSS 0 - 5.5 † (n = 183)	EDSS ≥ 6 (n = 65)	Age < 55 (n = 162)	Age ≥ 55 (n = 87)	Age ≥ 55 and EDSS ≥ 6 (n = 36)
Disease Breakthrough	8 (3%)	6 (3%)	2 (3%)	8 (5%)	-----	-----
Clinical Relapse w/ MRI Activity	5 (2%)	4 (2%)	1 (2%)	5 (3%)	-----	-----
Clinical Relapse w/o MRI Activity	2 (<1%)	2 (1%)	-----	2 (1%)	-----	-----
MRI Relapse w/o Clinical Activity	1 (<1%)	-----	1 (2%)	1 (<1%)	-----	-----
Subjects with ≥ 1 Moderate Infection Requiring Antibiotics	56 (22%)	38 (21%)	18 (28%)	33 (20%)	23 (26%)	11 (31%)
≥ 1 URI	22 (9%)	17 (9%)	5 (8%)	13 (8%)	9 (10%)	3 (8%)
≥ 1 LRI	5 (2%)	5 (3%)	-----	5 (3%)	-----	-----
≥ 1 UTI ♦	25 (10%)	11 (6%)	14 (22%)	12 (7%)	13 (15%)	7 (19%)
≥ 1 Other Infection ♦♦	16 (6%)	14 (8%)	2 (3%)	12 (7%)	4 (5%)	1 (3%)
Serious Infections (See Table 3)	6 (2%)	5 (3%)	1 (2%)	4 (2%)	2 (2%)	-----
HSV-1 / HSV-2	7 (3%)	4 (2%)	3 (5%)	3 (2%)	4 (5%)	2 (6%)
Zoster	4 (2%)	4 (2%)	-----	3 (2%)	1 (1%)	-----
Neoplasms▫	7 (3%)	6 (3%)	1 (2%)	1 (<1%)	4 (5%)	1 (3%)

† Sub-grouping failed to show significant difference ♦ 11 of these subjects reported a history of ≥ 1 UTI/year ♦♦ Including mastitis, cellulitis (3), dental abscess, impetigo, fungal vaginitis (2), otitis (3), conjunctivitis (2), strep pharyngitis (2), cutaneous abscess (4), stye.
▫ Neoplasms: colon carcinoma, breast papilloma, breast fibroadenoma, ovarian serous cystadenoma, adrenal adenoma, vulvar intraepithelial neoplasia, gastric polyp.

Conclusions

OCR and other anti-CD20 antibodies generally have an excellent safety profile, but long-term use has been associated with an increased risk of infections, the potential for hypogammaglobulinemia, and a possible increased risk of malignancy. The hypothesis in the ACAPELLA trial is that patients with higher levels of disability and/or older age may be at a higher risk.

Infections

Moderate infections requiring antibiotics were slightly more common in older and/or more disabled patients, but this was entirely driven by occurrence of UTIs. There was a trend suggesting patients over the age of 55 were more susceptible to herpes infections (5% compared to 2% age < 55). Six patients (2%) had serious infections requiring hospitalization, three of which occurred after the first infusion cycle (see Table 3), with no association to age or disability level.

Malignancy

Only one malignancy, Stage IIIb undifferentiated colon carcinoma, occurred in a 66-year old woman with PPMS, presenting 1 month after her cycle 3 infusion. Benign neoplasms were somewhat more frequent in patients age > 55, as might be expected.

Breakthrough Disease

Eight patients (3%), all age < 55, had disease breakthrough with clinical relapse and/or new MRI activity, similar to the rate observed in the clinical trials. 18 subjects (7%) 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, we did not see this. Other than an increased risk of UTIs in older and more disabled patients, other AEs occurred independent of age and EDSS level in patients who received 1-4 cycles of OCR. We have not observed a higher incidence of infection or new or recurrent cancers, although to date the number of patients treated for more than 18 months is too small to draw conclusions.

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. Perumal JS, Kister I, Howard J et al. Disease Exacerbation after Rituximab Induction in NMO, Neurology Neuroimmunology & Neuroinflammation, 2015 Feb 5, 2332-7812
4. Wehrum T, Beume LA, Stich O et al. Activation of Disease During Therapy with Alemtuzumab in 3 Patients with Multiple Sclerosis, Neurology, 2018 Feb 13, 1526-632X