DX22

ACAPELLA: Real World Experience with Ocrelizumab: An Observational Study Evaluating Safety in Patients with Relapsing and Progressive Multiple Sclerosis

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Background

Ocrelizumab (OCR) is a humanized monoclonal antibody that targets CD20+ B cells and is FDA approved for treatment of relapsing-remitting (RRMS) and primary progressive MS (PPMS). The pivotal Phase III clinical trials for RRMS (OPERA I/II) included only subjects ages 18-55 with EDSS of 0-5.5[1] and for the PPMS trial (ORATORIO), EDSS of 3-6.5[2]. ACAPELLA is a 5-year study exclusively sponsored by The Elliot Lewis Center in a real-world population receiving OCR.

Additional topics of interest include the impact on JCV antibody titers, immunoglobulin levels, and malignancy occurrence and outcomes in patients with or without a prior history. Interim analyses will continue to be conducted on a bi-annual basis.

Objectives

We sought to compare the frequency of adverse events (AEs) in our population with the clinical trial population (CTP), and to determine if AEs were more frequent in subjects with age and/or EDSS outside the inclusion criteria of the Phase III trials. This dataset reflects results at one year.

Methods

The study includes all subjects receiving commercial OCR at The Elliot Lewis Center. All subjects will be followed for 5 years. Assessments include EDSS, mammograms (standard of care), collection of medical history including history of benign or malignant cancers, exposure to immunosuppressive treatment, collection of AEs, JCV antibody with index, and immunoglobulins.

Results

- The study population as of 1 May 2018 includes 151 patients, 68 (45%) of whom were older than or had a higher EDSS score than those in the CTP.
- Baseline demographic and disease characteristics are reported in Table 1.

Results (cont.)

- 15 patients had a pre-existing history of cancer, see Table 3.
- The rates and severity of infusion-related reactions (IRRs) during and within 24 hours of infusion were comparable to the CTP.
- 14 patients had delayed IRRs, defined as occurring > 24 hours and ≤ 7 days post-infusion (13% of relapsing MS (RMS) population, 4% of progressive MS (PMS) population), detailed in Table 4.
- 4 patients had ongoing malaise lasting months (2 RMS, 2 PMS).
- 4 patients had clinical or MRI relapses, 3 of which were within 10 weeks of the first cycle (1 clinical relapse, 1 clinical and MRI relapse, and 2 MRI relapses).
- The infection rate was comparable to the CTP.
- One patient had an ectopic pregnancy 7 months following treatment.

Table 1: Total Population Demographics

	Relapsing Population	Progressive Population
Subjects	N = 95	N = 56
Mean Age	47	57
Female	78%	66%
Mean EDSS	3.0	5.2
Mean Years Since Dx	11	13
Hx Immunosuppressive Tx	11 (12%)	9 (16%)
Hx Malignancy ‡	8 (8%)	7 (13%)
Igs Available at Baseline	92 (97%)	52 (93%)
IgG < LLN at Baseline	8 (9%)	3 (6%)
IgM < LLN at Baseline	17 (18%)	14 (27%)

‡ Excludes basal cell carcinoma

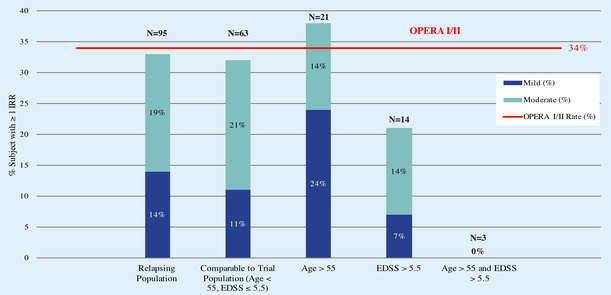
Table 2: DMT Prior to OCR

DMT	Relapsing (N=95)	Progressive (N=56)
No DMT w/in 1 year of OCR	14 (15%)	19 (34%)
Rituximab	4 (4%)	2 (4%)
Natalizumab: JCV Negative	7 (7%)	2 (4%)
Natalizumab: JCV Positive	10 (10%)	6 (11%)
Teriflunomide	9 (9%)	7 (13%)
Dimethyl Fumarate	16 (17%)	8 (14%)
Fingolimod	8 (8%)	2 (4%)
β-interferons	10 (11%)	2 (4%)
Glatiramer Acetate	17 (18%)	8 (14%)

Table 3: History of Malignancy

	Total Population (N=151)	Relapsing (N=95)	Progressive (N=56)
Breast Cancer	7 (5%)	2 (2%)	5 (9%)
Thyroid Cancer	3 (2%)	3 (3%)	0
Non-Hodgkin's Lymphoma	1 (1%)	1 (1%)	0
Prostate Cancer	1 (1%)	0	1 (2%)
Pituitary Cancer	1 (1%)	0	1 (2%)
Meningioma	2 (1%)	2 (2%)	0

Graph 1: IRR Occurrence in Relapsing Population



Graph 2: IRR Occurrence in Progressive Population

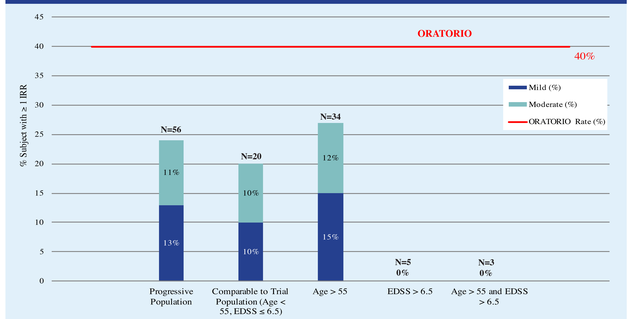


Table 4: AE Occurrence in Total Population

	Relapsing (N=95)	Progressive (N=56)
≥ 1 Infection	28 (29%)	11 (20%)
≥ 1 URI	15 (16%)	5 (9%)
≥ 1 UTI	6 (6%)	3 (5%)
LRI	3 (3%)	1 (2%)
Zoster	2 (2%)	0
Other Infection	2 (2%)†	2 (4%)††
IRR ◊	31 (33%)	13 (23%)
Delayed IRR ◊◊	12 (13%)	2 (4%)
Clinical Relapse	2 (2%)	-----

†Yeast Infection (1), Tooth Infection (1)
◊Within 24 hours of infusion
††Yeast Infection (1), Mastitis (1)
◊◊> 24 hours and ≤ 7 days post-infusion

Conclusions

OCR is a high potency treatment indicated for both RRMS and PPMS. Treatment with OCR and other anti-CD20 antibodies has been associated with an increased risk of infections, the potential for hypogammaglobulinemia, and a possible increased risk for certain types of cancers. While the Phase III clinical trials for OCR showed a favorable safety profile, real-world experience may uncover different safety signals. Importantly, we had a small but significant number of patients with early clinical and/or MRI relapses. In the CTP, the earliest MRIs were done at 24 weeks; early asymptomatic MRI activity would have been missed. An increase in inflammatory activity post-infusion, as seen in 4 patients, has been reported after initiation of other anti-B-cell therapies[3,4], and offers a putative explanation for the delayed IRRs and/or prolonged malaise observed in 17 patients. The frequency of both asymptomatic early MRI breakthrough and relapses observed in ACAPELLA suggests this may be more common than previously appreciated, but as of yet the numbers are too small to suggest possible risk factors or longer-term significance.

Although our presumption was that older and/or more disabled patients might have higher rates of AEs, we did not see this in our patients. While it is premature to compare the risk of infections and cancer in our population directly to the CTP, we have not observed a higher incidence of infections nor have we seen any new or recurrent cancers. As a whole, our population's rate of IRRs was comparable to the CTP, but we also observed previously undescribed delayed infusion reactions, and/or prolonged malaise that mimicked disability progression in a small population of patients.

References

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