A real-life, multicenter, observational study to evaluate safety and efficacy of the switch from alemtuzumab to ocrelizumab in MS patients with evidence of disease activity/progression after two alemtuzumab courses: the Italian experience

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INTRODUCTION

Therapeutic sequencing after high-efficacy induction treatments is a matter of debate in MS. No safety and efficacy data about the switch to ocrelizumab (OCR) in patients (pts) with evidence of disease activity/progression after two alemtuzumab (ALM) courses have been reported yet.

AIMS

To evaluate safety and efficacy of the switch from ALM to OCR in an Italian, multicentric cohort of MS patients with evidence of disease activity and/or progression after two ALM courses.

METHODS

Descriptive results were reported as mean with standard deviation (SD) or median with interquartile range (IQR). The probability of disability worsening-free survival, relapsefree survival, MRI activity-free survival, and NEDA-3 status was calculated with the Kaplan–Meier estimator. Univariate and multivariate analyses assessing the association of demographic- and disease-related characteristics with survival endpoints were performed using Cox proportional hazards regression analysis models. Differences in lymphocyte subpopulations and immunoglobulins at different timepoints were assessed with analysis of covariance, adjusting for age, sex, time between II ALM course and OCR start. Correction was made for multiple comparisons.

RESULTS

Patients, n.	**72**
Age at OCR start, mean (SD), years	39.1 (9.2)
Gender, female (%)	63.9
MS phenotype at OCR start, %	
RRMS	79.2
PnoRMS[1]	6.9
RPMS[2]	13.9
DMTs pre-ALM	
naïve, %	12.5
I-line, %	27.8
fingolimod, %	40.3
natalizumab, %	23.6
Cumulative n. of relapses after ALM, mean	69
N. of new T2 lesions at MS reactivation after ALM, mean (SD)	3 (3.2)
N. of Gd+ lesions at MS reactivation after ALM, mean (SD)	1 (2)
Time between last ALM and OCR start, mean (SD), months	29 (11.6)
Disease duration at OCR start, mean (SD), years	12.4 (6.7)
FU duration from OCR start, mean (SD), years	2.4 (1)
EDSS at ALM start, median (IQR)	4 (1-8)
EDSS at OCR start, median (IQR)	3.5 (0-8)

only patients with at least 6-months FU were enrolled. [1] MS patients who showed disability progression (defined a confirmed EDSS increase) without evidence of relapse and/or MRI activity. [2] Relapsing Progressing MS

Adverse Events

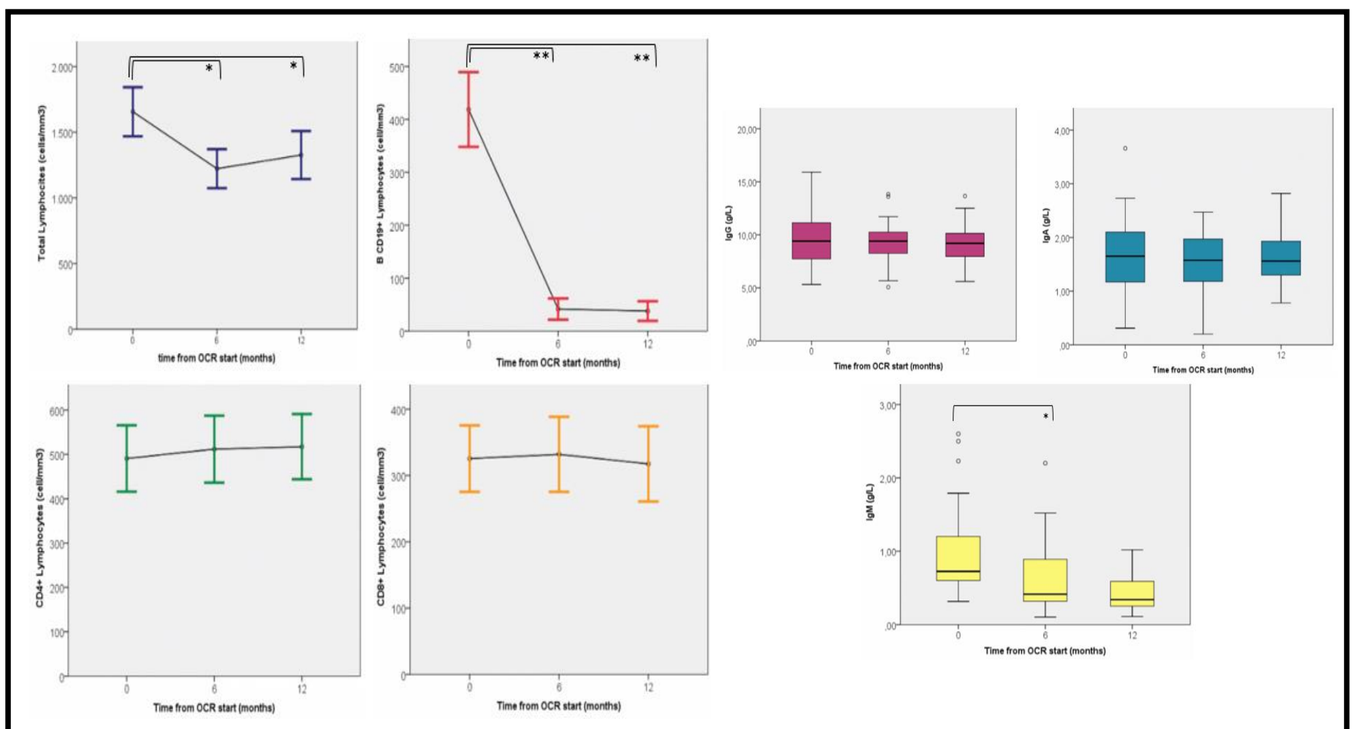
	Total cohort	RRMS	PnoRMS/RPMS
Any adverse events, n (%)			
Adverse events leading to OCR discontinuation, n (%)	1(1.4)[1]	1 (1.7)	0
Pregnancy leading to OCR discontinuation, n (%)	1 (1.4)	1 (1.7)	0
Adverse events leading to hospitalization, n (%)	2[2] (2.8)	0	2 (13.3)
Number of adverse events per subject, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)
Time from first OCR infusion, months	184 (67-456)	135 (67-404)	201 (67-487)
Serious infusion associated reactions, n (%)	0	0	0
Infectious adverse events, n (%)			
Pneumonia	1	1	0
Upper respiratory tract infection	35	15	20
Lower urinary tract infection	9	4	5
HSV1 reactivation	7	4	3
VZV reactivation	3	2	1
Neoplasm, n (%)	2[3] (2.8)	1 (1.7)	1 (6.7)
Death, n (5)	0	0	0

[1] colic cancer, treated with surgery and chemotherapy

[2] appendicectomy (1), colic cancer (1)

[3] colic cancer (1), CIN2 (1)

Lymphocytes and Immunoglubulins (n=33)



A significant decrease in total lymphocytes count was observed between OCR start and 6-months FU (1648.5±841.2 cell/mm^3 vs 1178±392.9 cell/mm^3, mean difference= 470.5, 95% CI [97.6, 843.6], p=0.010) and between OCR start and 12-months FU (1648.5±841.2 cell/mm^3 vs 1285.6 ±517.4 cell/mm^3, mean difference= 362.9, 95% CI [11.3, 714.5], p=0.041).

Twenty-four (72.7%) MS patients showed **TCD4+** lymphopenia at OCR start (363.2±15.4 cell/mm^3). **No significant differences in TCD4+ lymphocytes** were observed at the same timepoints.

Eleven (33.3%) MS patients showed **TCD8+** lymphopenia at OCR start (165.2±15.4 cell/mm^3). **No significant differences in TCD8+ lymphocytes were observed at the same timepoints**

None of MS patients showed **BCD19+** lymphopenia at OCR start, while 8 (24.2%) showed BCD19+ lymphocytosis. **A significant decrease in BCD19+ lymphocytes count was observed between OCR start and 6-months FU** (415.9±46.1 cell/mm^3 vs 36.8±10.5 cell/mm^3, mean difference= 379.1, 95% CI [264.3, 493.9], p<0.001) and between OCR and 12-months FU (36.8±10.5 cell/mm^3 vs 28.3±8.5 cell/mm^3, mean difference= 37.6, 95% CI [269.3, 505.9], p<0001). This finding was confirmed also MS patients who had BCD19+ lymphocytosis at OCR start (p<0.05).

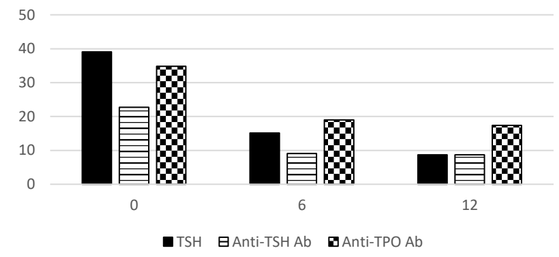
A subgroup analysis was performed on MS patients who reached 2years-FU (n=16). **A significant increase in T CD4+ lymphocytes was observed between 12-months and 24-months FU** (532.5±47.7 cell/mm^3 vs 634.1±49.8 cell/mm^3, mean difference= -101.6, 95% CI [-263.1, 59.9], p<0.05). B CD19+ cells depletion was maintained also at 24-months FU.

None of the patients showed hypo-IgG, hypo-IgA nor hypo-IgM at OCR start. No significant differences in IgG and IgA were observed. **A significant decrease in IgM levels was observed between OCR start and 6-months FU** (0.9±0.1 g/L vs 0.6±0.1 g/L, mean difference= 0.345, 95% CI [0.2, 0.5], p<0.001). Hypo-IgM was stable at 12-months FU (0.6±0.1 g/L) (48.1% of patients)

Autoimmunity

None of MS patients showed new ALM-related autoimmune events (thyroiditis 1-month later OCR start).

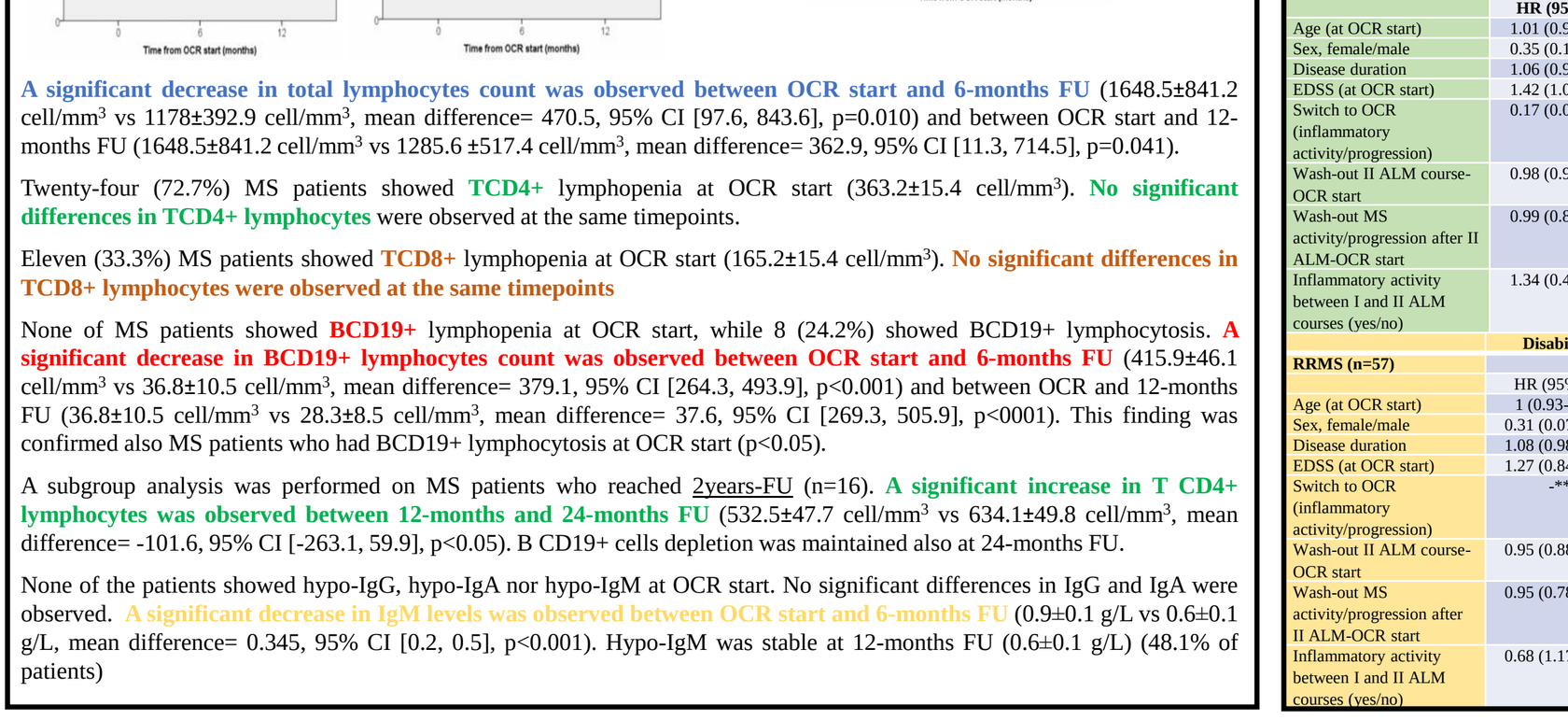
At 6-months and 12-months FU a decrease in the percentage of MS patients who showed TSH abnormalities (hypo/hyper), anti-TSH antibodies positivity and anti-TPO antibodies positivity was observed. One patient otherwise candidate at thyroidectomy showed a rapid normalization of thyroid function and at 6-months FU stopped any thyroid treatment.



Efficacy

Univariate and Multivariate Analyses of Factors Associated with Outcomes

	Disability worsening		MRI-inflammatory activity		Relapse		NEDA-3 status	
Total Cohort (n=72)								
	HR (95% CI)	**p val**	**HR (95% CI)**	**p val**	**HR (95% CI)**	**p val**	**HR (95% CI)**	**p val**
Age (at OCR start)	1.01 (0.96-1.07)	0.54	0.96 (0.88-1.05)	0.43	0.01 (0.92-0.11)	0.87	1.01 (0.96-1.07)	0.56
Sex, female/male	0.35 (0.11-1.05)	0.06	0.87 (0.19-3.91)	0.86	0.93 (0.16-5.59)	0.94	0.53 (0.22-1.28)	0.16
Disease duration	1.06 (0.99-1.14)	0.09	0.93 (0.81-1.07)	0.38	0.94 (0.79-1.11)	0.46	1.03 (0.96-1.09)	0.39
EDSS (at OCR start)	1.42 (1.06-1.92)	**0.02**	0.82 (0.55-1.21)	0.31	0.87 (0.56-1.36)	0.55	1.16 (0.93-1.45)	0.18
Switch to OCR (inflammatory activity/progression)	0.17 (0.05-0.59)	**0.005**	-*	-*	-*	-*	0.45 (0.14-1.41)	0.17
Wash-out II ALM course-OCR start	0.98 (0.93-1.04)	0.58	1.01 (0.94-1.08)	0.82	0.99 (0.91-1.08)	0.91	0.99 (0.95-1.04)	0.81
Wash-out MS activity/progression after II ALM-OCR start	0.99 (0.88-1.11)	0.86	0.87 (0.67-1.12)	0.29	0.91 (0.71-1.17)	0.48	0.96 (0.86-1.07)	0.47
Inflammatory activity between I and II ALM courses (yes/no)	1.34 (0.45-4.01)	0.60	0.09 (0.01-0.79)	**0.03**	1.15 (0.02-1.31)	**0.08**	0.53 (0.21-1.31)	0.17
	Disability worsening		**MRI-inflammatory activity**		**Relapse**		**NEDA-3 status**	
RRMS (n=57)								
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age (at OCR start)	1 (0.93-1.08)	0.96	0.98 (0.89-1.08)	0.73	1.03 (0.93-1.14)	0.52	1.01 (0.94-1.07)	0.84
Sex, female/male	0.31 (0.07-1.29)	0.11	0.75 (0.17-3.37)	0.75	0.81 (0.14-4.88)	0.82	0.54 (0.18-1.53)	0.24
Disease duration	1.08 (0.98-1.19)	0.10	0.96 (0.84-1.11)	0.61	0.97 (0.82-1.14)	0.72	1.03 (0.96-1.12)	0.39
EDSS (at OCR start)	1.27 (0.84-1.89)	0.25	0.98 (0.63-1.52)	0.92	1.07 (0.64-1.79)	0.79	1.12 (0.83-1.53)	0.46
Switch to OCR (inflammatory activity/progression)	-**	-**	-**	-**	-**	-**	-**	-**
Wash-out II ALM course-OCR start	0.95 (0.88-1.02)	0.18	1.01 (0.94-1.07)	0.87	0.99 (0.91-1.08)	0.87	0.98 (0.94-1.03)	0.53
Wash-out MS activity/progression after II ALM-OCR start	0.95 (0.78-1.15)	0.58	0.90 (0.71-1.14)	0.38	0.94 (0.75-1.17)	0.56	0.92 (0.79-1.07)	0.29
Inflammatory activity between I and II ALM courses (yes/no)	0.68 (1.17-2.74)	0.58	0.08 (0.01-0.64)	**0.02**	0.12 (0.01-1.07)	**0.05**	0.26 (0.08-0.78)	**0.01**



CONCLUSIONS

- the switch to OCR after 2 ALM courses is safe, no differences in terms of infections and others AEs with respect to clinical trials and real-lie available findings were observed
- IgM seemed to decrease rapidly in 48.1% patients at 6 and 12-months FU with no effects on IgG levels, but a longer FU is needed
- OCR after ALM seemed to not deeply influence TCD4+ profile and repopulation at 2y FU
- BCD19 cells depletion occurred also in MS patients with evidence of hyper-BCD19 cell at OCR start.
- Inflammatory activity (relapse and/or MRI activity) between the first and second ALM course was associated with a higher risk of relapse and MRI activity during OCR treatment. This finding was confirmed also analysing RRMS subgroup separately. No impact on EDSS seemed to emerge, but a longer FU is needed.
- EDSS at OCR start and the evidence of disability progression (without relapses and/or MRI activity) after II ALM course as leading cause of OCR start were associated with an increased risk of disability worsening during OCR treatment in the whole cohort.
- At 2-year FU, NEDA-3 percentages were 79.9%, 82.1% and 72.7% for the whole cohort, RRMS and PMS respectively