Efficacy of Ofatumumab in Treatment-Naïve, First-Switch, and Late-Switch Patients: Insights From the ALITHIOS Open-Label Extension Study

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Background

- Early initiation of high-efficacy therapies for relapsing multiple sclerosis (RMS) has been shown to improve longer-term outcomes versus initiation of or escalation from low-efficacy therapies[1-3]
- Ofatumumab, a fully human anti-CD20 monoclonal antibody, reduced annualized relapse rate (ARR), magnetic resonance imaging (MRI) lesion activity, and delayed disability worsening versus teriflunomide in RMS patients who were treatment-naïve (TN) or previously treated (PT) with disease-modifying therapies (DMTs) in Phase 3 ASCLEPIOS I and II trials[4,5]
- Ofatumumab was well tolerated for up to 4 years of treatment with no new safety risks identified[6-8]
- All ASCLEPIOS patients entering the ALITHIOS extension study were switched to open-label ofatumumab, allowing further insights into ofatumumab efficacy in TN or PT patients and after first and late DMT switch

Objective

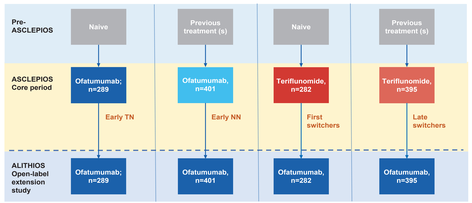
- To compare efficacy (clinical and MRI) and safety outcomes in patients initiating ofatumumab early versus switching to ofatumumab after one or multiple previous DMTs in the ASCLEPIOS I and II and ALITHIOS studies

Methods

Study design and patient population

- This analysis included cumulative data from patients randomized to ofatumumab or teriflunomide in the ASCLEPIOS I and II trials (core study) and continued on ofatumumab in the ALITHIOS open-label extension study
- Of 1882 patients randomized in the ASCLEPIOS I and II trials, 1367 (72.6%) patients enrolled into the ALITHIOS open-label extension study and received ofatumumab for up to 4 years

Figure 1. Patient disposition



Prior DMTs before enrollment in ASCLEPIOS I and II were any interferon beta, glatiramer acetate, and dimethyl fumarate
NN, non-naïve; TN, treatment-naïve

- Patients were analyzed in four treatment groups **(Figure 1)**:
  - **Early treatment-naïve (early TN)**: TN patients randomized to ofatumumab in ASCLEPIOS I and II and continued ofatumumab in ALITHIOS
  - **Early non-naïve (early NN)**: Patients who were PT, randomized to ofatumumab in ASCLEPIOS I and II, and continued ofatumumab in ALITHIOS
  - **First switchers**: TN patients randomized to teriflunomide in ASCLEPIOS I and II and switched to ofatumumab in ALITHIOS
  - **Late switchers**: Patients PT with ≥1 DMTs, randomized to teriflunomide in ASCLEPIOS I and II, and switched to ofatumumab in ALITHIOS

Key assessments

- Outcomes in ASCLEPIOS I and II (up to 30 months treatment) were compared with outcomes over 18 months in ALITHIOS (i.e., post-switch to open-label OMB)
- ARR
- 6-month confirmed disability worsening (6mCDW)
  - Confirmed disability worsening is defined as an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 6 months
- Brain MRI outcomes
  - Mean number of gadolinium-enhancing (Gd+) T1 lesions per scan
  - Number of new or enlarging T2 (neT2) lesions per year
- Safety outcomes were analyzed in long-term safety set which includes all patients who received at least one dose of ofatumumab either in the core studies (ASCLEPIOS I and II, APLIOS and APOLITOS) or in the ALITHIOS, open-label extension study.

Results

Baseline characteristics

- At baseline (before entering ASCLEPIOS), mean age of patients was approximately 39 years across all the treatment groups; majority of patients were women (>65%) **(Table 1)**
- Mean EDSS score at baseline was approximately 2.8 across all the treatment groups

Table 1. Baseline demographics and disease characteristics

Demographics and Clinical Characteristics[a]	Early TN N=289	Early NN N=401	First Switchers		Late switchers	
			Core phase; N=282	Extension phase; N=282	Core phase; N=395	Extension phase; N=395
Age, years	37.8±9.16	38.3±8.35	36.9±9.15	38.9±9.16	39.0±9.18	41.0±9.16
Female, n (%)	207 (71.6)	276 (68.8)	185 (65.6)	185 (65.6)	271 (68.6)	271 (68.6)
BMI, kg/m²	25.82±6.16	25.28 ±5.83	25.64±5.48	25.68±5.33	25.58±6.11	25.70 ±6.17
EDSS score at baseline	2.43 ±1.25	3.19±1.33	2.34±1.21	2.36±1.32	3.08±1.31	3.13±1.47
Time since diagnosis of MS, years	2.26±4.18	7.84±6.01	2.13±4.20	4.01±4.20	7.83±5.97	9.7±5.99
Number of relapses in the last 12 months prior to screening	1.3±0.75	1.2±0.61	1.3±0.65	0.1±0.40	1.2±0.70	0.2±0.54
Number of Gd+ T1 lesions	1.8 ±4.53	1.7±4.78	1.3±2.74	0.6±1.85	1.2±3.92	1.0±2.67
Total volume of T2 lesions, cm^3	11.44±13.03	15.27±13.75	9.68±10.27	-	14.47±14.78	-

[a]Values are represented as mean±SD unless specified otherwise.
BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; SD, standard deviation.

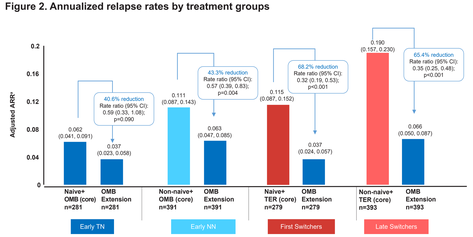
Annualized relapse rate

- ARR in patients who received early ofatumumab treatment (early NN and early TN) was lower compared with patients who were switched from teriflunomide (first switchers and late switchers)
- Continuous use of ofatumumab was associated with a reduction in ARR by 40.6% in the early TN group and by 43.3% in the early NN group, while switch from teriflunomide to ofatumumab resulted in a pronounced reduction in ARR (68.2% in first switchers and 65.4% in late switchers) **(Figure 2)**
- Regardless of the timing of ofatumumab treatment initiation, a significant reduction in ARR was observed across all four treatment groups

6-month confirmed disability worsening

- Continuous use of ofatumumab was associated with less number of CDW events when initiated early. Pronounced reduction of events was observed when patients switched from teriflunomide with the least benefit observed in late switchers **(Table 2)**

Figure 2. Annualized relapse rates by treatment groups



[a]Obtained from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesions and the patient's age at baseline as covariates. The natural log of the time-in-study (in years) by period is used as offset to annualize the relapse rate in each period; ARR, annualized relapse rate; CI, confidence interval; early NN, early non-naïve; early TN, early treatment naïve; OMB, ofatumumab; TER, teriflunomide.

Table 2. KM estimates of the proportions with 6mCDW at various timepoints

		KM estimate with event, %	
		Month 18 %, (95% CI)	n/ N (%)
Early TN	Core phase[a]	5.6 (3.5, 9.0)	17/289 (5.9)
	Extension phase[b]	3.4 (1.8, 6.5)	9/287 (3.1)
Early NN	Core phase[a]	7.8 (5.5, 10.9)	31/401 (7.7)
	Extension phase[b]	7.7 (5.4, 10.8)	29/397 (7.3)
First switchers	Core phase[a]	7.1 (4.7, 10.8)	20/282 (7.1)
	Extension phase[b]	4.1 (2.3, 7.4)	11/281 (3.9)
Late switchers	Core phase[a]	9.7 (7.2, 13.1)	42/395 (10.6)
	Extension phase[b]	7.1 (5.0, 10.2)	30/392 (7.7)

[a]ASCLEPIOS up to Month 18; [b]ALITHIOS (post switch to ofatumumab) up to Month 18; early NN, early non-naïve; early TN, early treatment naïve; KM, Kaplan Meier; n=number of patients with events; N=Total number of patients in the group.

MRI lesion activity

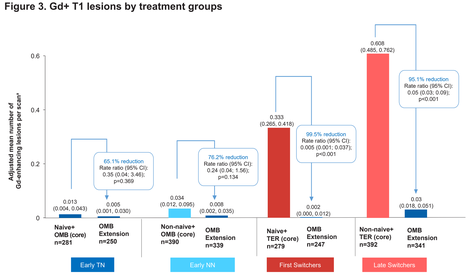
Mean number of Gd+ T1 lesions per scan

- Mean number of Gd+ T1 lesions in patients who received early ofatumumab treatment (early NN and early TN) was lower compared with patients who were switched from teriflunomide (first switchers and late switchers)
- Despite a reduced lesion load in early TN and early NN patients, a reduction of 65.1% and 76.2%, respectively, was observed
- An almost complete suppression of Gd+ T1 lesion activity was observed in first and late switchers (99.5% and 95.1%, respectively) **(Figure 3)**

Number of neT2 lesions per year

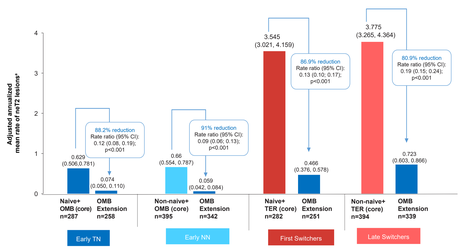
- Mean number of neT2 lesions in patients who received early ofatumumab treatment (early NN and early TN) was lower compared with patients who were switched from teriflunomide (first switchers and late switchers)
- Despite a reduced lesion load in early TN and early NN patients, a significant reduction of 88.2% and 91%, respectively was observed
- A similar significant reduction in neT2 lesion activity was observed in first and late switchers (86.9% and 80.9%, respectively) **(Figure 4)**

Figure 3. Gd+ T1 lesions by treatment groups



[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, baseline number of T1 Gd+ lesions and patient's age at baseline as covariates. The natural log of the number of scans with evaluable Gd-enhancing lesion counts by period is used as offset to obtain the lesion rate per scan in each period. Baseline variables are from the core study baseline; CI, confidence interval; early NN, early non-naïve; early TN, early treatment naïve; Gd, gadolinium; OMB, ofatumumab; TER, teriflunomide.

Figure 4. neT2 lesions by treatment groups



[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment as factor, baseline volume of T2 lesions and patient's age at baseline as covariates. The natural log of the time-in-study (in years) by period is used as offset to annualize the lesion rate in each period. Baseline variables are from the core study baseline. All P values are nominal P values; CI, confidence interval; early NN, early non-naïve; early TN, early treatment naïve; neT2, new or enlarging T2; OMB, ofatumumab; TER, teriflunomide.

Safety outcomes

- The proportion of patients with ≥1 AE with ofatumumab in early TN, early NN, first switchers, and late switchers was 94.1%, 92.5%, 82.6%, and 80.3%, respectively
- Infection rates observed in early TN, early NN, first switchers, and late switchers were 73.7%, 68.1%, 50.7%, and 53.2%, respectively
- Most common AEs were injection-related reaction, COVID-19, nasopharyngitis **(Table 3)**
- Across all the treatment groups, both mean IgG and IgM were above the lower limit of normal (LLN) for majority of patients
  - IgG levels: early TN: 99.3%, early NN: 98.3%, first switchers: 99.6%, late switchers: 98.2%
  - IgM levels: early TN: 70.6%, early NN: 70.3%, first switchers: 79%, late switchers: 72.9%

Table 3. Most common TEAEs[a] (>10% in any group)

Event, n (%)	Early TN, N=289	Early NN, N=401	First Switchers, N=282	Late Switchers, N=395
Any AE	272 (94.1)	371 (92.5)	233 (82.6)	317 (80.3)
Injection-related reaction	79 (27.3)	105 (26.2)	67 (23.8)	88 (22.3)
COVID-19	37 (12.8)	48 (12.0)	39 (13.8)	47 (11.9)
Nasopharyngitis	89 (30.8)	86 (21.4)	41 (14.5)	40 (10.1)
Urinary tract infection	34 (11.8)	77 (19.2)	13 (4.6)	36 (9.1)
Upper respiratory tract infection	47 (16.3)	64 (16.0)	23 (8.2)	38 (9.6)
IgM decreased	44 (15.2)	59 (14.7)	24 (8.5)	51 (12.9)
Headache	63 (21.8)	55 (13.7)	23 (8.2)	26 (6.6)
Injection-site reaction	49 (17.0)	50 (12.5)	28 (9.9)	30 (7.6)
Backpain	37 (12.8)	44 (11.0)	18 (6.4)	18 (4.6)
Arthralgia	32 (11.1)	34 (8.5)	13 (4.6)	19 (4.8)
Diarrhea	20 (6.9)	35 (8.7)	34 (12.1)	50 (12.7)
Alopecia	16 (5.5)	30 (7.5)	5 (1.8)	11 (2.8)
Fatigue	40 (13.8)	31 (7.7)	11 (3.9)	16 (4.1)
Hypertension	14 (14.8)	27 (6.7)	2 (0.7)	11 (2.8)

[a]Data from the time of the first dose of the ofatumumab is included; aTEAEs is defined as any AE which started on or after the day of the first dose of the study medication; AEs occurring at any time during the course of the 4 year period; AE, adverse event; COVID-19, corona virus disease; Ig, immunoglobulin; TEAE, treatment emergent AE.

Conclusions

- These results show consistent efficacy in reducing relapses, MRI lesion activity, and the risk of disability worsening observed in early and treatment naïve vs switching from other DMTs, highlighting the value of earlier initiation of ofatumumab in patients with RMS
- Early use of ofatumumab either as first or second line of therapy is beneficial in patients compared to later switchers
- Ofatumumab treatment was well-tolerated across all subgroups of patients and the safety findings were consistent with the overall ASCLEPIOS I and II study populations

References

1. He A, et al. *Lancet Neurol*. 2020;19:307–316;
2. Harding K, et al. *AMA Neurol*. 2019;76:536–541;
3. Iaffaldano P, et al. *Ther Adv Neurol Disord*. 2021;14:17562864211019574;
4. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed March 29, 2022);
5. Hauser SL, et al. *N Engl J Med*. 2020;383:546–57
6. Hauser SL. oral presentation presented at AAN 2022; S14.004

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