Effect of Ofatumumab on Lymphocytes and Neutrophils in Patients With Relapsing Multiple Sclerosis up to 4 Years

DMT11

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Background

- Ofatumumab, a fully human anti-CD20 monoclonal antibody, administered monthly as a 20 mg subcutaneous (s.c.) injection is approved for the treatment of relapsing multiple sclerosis (RMS) in adults[1]
- Ofatumumab binds to a unique conformational epitope which confers it a higher potency compared with other anti-CD20s, depleting B cells more efficiently and allowing for s.c. administration at lower doses[2]
- The low s.c. dosing regimen for ofatumumab has been designed to result in fast B-cell depletion (3 times 20 mg weekly) and maintain constant near complete B-cell depletion (monthly 20 mg) with long-term use in patients with RMS, while avoiding the use of high doses[2]
- Higher doses of anti-CD20 therapies in non-MS indications have been associated with lymphopenia, neutropenia,[3,4] and an increased risk of infections[4]
- In RMS patients in the Phase 3 ASCLEPIOS I/II trials, treatment with ofatumumab 20 mg s.c. for up to 30 months had a favourable safety profile, was generally well tolerated with no increase in risk of lymphopenia or neutropenia[5,6]
- Assessment of the long-term safety of ofatumumab is important to further understand its benefit-risk profile

Objective

- To assess the longer-term effect of ofatumumab on lymphocyte and neutrophil levels up to 4 years and its association with the risk of serious infections during the core and open-label extension studies in RMS patients

Methods

Patient population

- Patients completing the core ASCLEPIOS I/II, APOLITOS and APLIOS clinical trials could enter ALITHIOS, an ongoing, open-label, umbrella extension trial
- Cumulative data on lymphocyte and neutrophil levels for up to 4 years of ofatumumab treatment were analyzed in the following three groups (Data cut-off: 25-Sep-2021)
  - The **overall safety population** included 1969 patients, of whom 1292 were in the continuous ofatumumab group and 677 in the newly switched ofatumumab group
  - **Continuous ofatumumab**: Patients who were treated with ofatumumab in the core studies (ASCLEPIOS I/II, APLIOS, or APOLITOS), regardless of whether they entered ALITHIOS
  - **Newly switched ofatumumab**: Patients who were randomized to teriflunomide in ASCLEPIOS I/II and switched to ofatumumab on entering ALITHIOS
- Safety data from first dose of ofatumumab till last dose date +100 days (or by the data cutoff, if earlier) were included

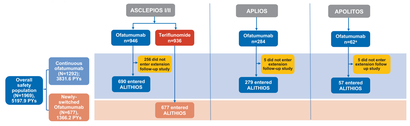
Assessments

- Serum lymphocyte and neutrophil levels were measured every 12 weeks in the core studies and every 12 weeks up to Week (W) 48, and then every 24 weeks thereafter in the extension
- Mean absolute lymphocyte and neutrophil levels from baseline up to W216 and percent change from baseline in lymphocyte and neutrophil levels were analyzed
  - Assessments from treatment start date in core study up to last dose date + 100 days (or by the data cutoff, if earlier) are considered in the analysis
  - All assessments contribute to the calculation of mean irrespective of whether patient had treatment interruption or discontinuation
- The proportions of patients with levels below lower limit of normal [LLN (10^9/L): lymphocytes, 0.91; neutrophils, 1.96] at least once or twice consecutively post-baseline and their association with the incidence rate (per 100 patient-years) of serious infections were assessed
- Incidence, severity, and outcomes of lymphopenia and neutropenia that were reported as adverse events were analyzed
- Incidence rate and 95% confidence intervals (CI) were estimated by Poisson regression where patients were censored at time of first event
- Serious infections occurring within 1 month prior and until 1 month after any detection of drop in lymphocytes or neutrophils below LLN were also reported

Results

- In the overall safety population, 86.5% patients (1703/1969) completed core studies and entered ALITHIOS. Of these, 88.5% patients (1508/1703) were still receiving ofatumumab treatment at the time of data cutoff (25-Sep-2021), **Figure 1**

Figure 1. Patient population

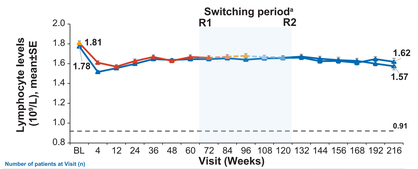


[a]Patients were either randomized to or switched to ofatumumab during the core study

Change in lymphocyte levels up to 4 years

- In both continuous and switch groups, an initial slight and transient decline in mean lymphocyte levels was observed up to W4 (%change at W4: continuous, −11.9%; switch, −8.2%)
- Later, mean lymphocyte levels showed a reversal and then stabilized in the long-term up to W216 (**Figure 2**)

Figure 2. Mean lymphocyte levels with ofatumumab up to 4 years



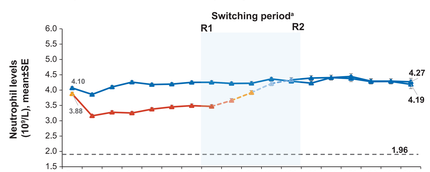
Number of patients at Visit (n)																	
Continuous OMB	1292	1266	1264	1238	1194	1141	1086	901	982	776	915	632	595	448	341	431	475	205
	677	670	674	668	670	665	670	671	631	631	634	553	475	421	326	432	441	180
Before/ After switch	677	670	674	668	670	665	670	665 / 06	480 / 151	313 / 318	170 / 464	72 / 481	475	421	326	432	441	180

[a]Switching period refers to the patients started with teriflunomide and not applicable to the patients with ofatumumab in core period; For TER/OMB group, data from 1st dose of TER until last dose of OMB plus 100 days/ analyses cut-off date have been used; R1: The first patient with first treatment emergent assessment in OMB period after switching to OMB (72 weeks); R2: The last patient with last treatment emergent assessment in TER period before switching to OMB (120 weeks); BL, baseline; LLN, lower limit of normal; IR, incidence rate; OMB, ofatumumab; SE, standard error of the mean; TER, teriflunomide.

Change in Neutrophil levels up to 4 years

- In the continuous group, mean neutrophil levels remained stable and above baseline for all visits up to W216
- In the switch group, mean neutrophil levels decreased up to W4 and remained low during pre-switch period (teriflunomide use[a]) followed by a reversal and stabilization (reaching baseline levels) post-switch (**Figure 3**)

Figure 3. Mean neutrophil levels with ofatumumab up to 4 years



Number of patients at Visit (n)																	
Continuous OMB	1292	1266	1264	1238	1195	1142	1087	901	982	776	915	632	595	448	341	431	475	205
TER/OMB	677	670	674	668	670	667	670	671	631	631	634	553	475	421	326	432	441	180
Before/ After switch	677	670	674	668	670	667	670	665 / 06	480 / 151	313 / 318	170 / 464	72 / 481	475	421	326	432	441	180

[a]Switching period refers to the patients started with teriflunomide and not applicable to the patients with ofatumumab in core period; For TER/OMB group, data from 1st dose of TER until last dose of OMB plus 100 days/ analyses cut-off date have been used; R1: The first patient with first treatment emergent assessment in OMB period after switching to OMB (72 weeks); R2: The last patient with last treatment emergent assessment in TER period before switching to OMB (120 weeks); TER is known to cause a decrease in white blood cells (mainly neutrophils and lymphocytes)[7]

BL, baseline; LLN, lower limit of normal; IR, incidence rate; OMB, ofatumumab; SE, standard error of the mean; TER, teriflunomide.

- Up to 4 years, the overall proportion of patients with levels below LLN (lymphocytes, 0.91X10^9/L; neutrophils, 1.96X10^9/L) at least once or twice consecutively were 17.9% (352/1965) and 5.9% (116/1965) for lymphocytes, respectively, and 13.6% (267/1965) and 3.1% (60/1965) for neutrophils, respectively
- The majority of drops in levels below LLN or respective Common Terminology Criteria for Adverse Events (CTCAE) grades were single occurrences and not sustained over a longer period (**Table 1**)

Table 1. Summary of Lymphocytes or Neutrophils below different cut-off values as per CTCAE grades at least once or consecutively twice post–baseline

CTCAE Grade (Cut-off [x10^9/L])	Time-point	Continuous ofatumumab N=1292 n/M (%)	Newly switched ofatumumab N=677 n/M (%)	Overall safety population N=1969 n/M (%)
Lymphocytes				
Grade ≥1 (<0.91)	At least once post-baseline	278/1290 (21.6)	74/675 (11.0)	352/1965 (17.9)
	Consecutively twice post-baseline	95/1290 (7.4)	21/675 (3.1)	116/1965 (5.9)
Grade ≥2 (<0.8)	At least once post-baseline	116/1290 (9.0)	35/675 (5.2)	151/1965 (7.7)
	Consecutively twice post-baseline	26/1290 (2.0)	6/675 (0.9)	32/1965 (1.6)
Grade ≥3 (<0.5)	At least once post-baseline	12/1290 (0.9)	4/675 (0.6)	16/1965 (0.8)
	Consecutively twice post-baseline	0	1/675 (0.1)	1/1965 (0.1)
Grade 4 (<0.2)	At least once post-baseline	1/1290 (0.1)	0	1/1965 (0.1)
	Consecutively twice post-baseline	0	0	0
Neutrophils				
Grade ≥1 (<1.96)	At least once post-baseline	217/1290 (16.8)	50/675 (7.4)	267/1965 (13.6)
	Consecutively twice post-baseline	50/1290 (3.9)	10/675 (1.5)	60/1965 (3.1)
Grade ≥2 (<1.5)	At least once post-baseline	70/1290 (5.4)	10/675 (1.5)	80/1965 (4.1)
	Consecutively twice post-baseline	5/1290 (0.4)	2/675 (0.3)	7/1965 (0.4)
Grade ≥3 (<1.0)	At least once post-baseline	21/1290 (1.6)	1/675 (0.1)	22/1965 (1.1)
	Consecutively twice post-baseline	0	0	0
Grade 4 (<0.5)	At least once post-baseline	6/1290 (0.5)	0	6/1965 (0.3)
	Consecutively twice post-baseline	0	0	0

Assessments from the first dose of ofatumumab, up to and including last dose + 100 days are included.
CTCAE, Common Terminology Criteria for Adverse Events; N, the total number of patients in the treatment group; n, Number of patients who are at the corresponding category; M, Number of patients with non-missing baseline and at least one not missing post baseline value for the parameter.

Incidence, severity and outcomes of lymphopenia and neutropenia adverse events

- In the overall safety population, the incidence rate (95% CI) of lymphopenia and neutropenia AEs remained low (0.31 [0.19, 0.51] for both) and was consistent with the incidence reported in the core trials (0.19 [0.06; 0.59])
- Most events were of Grade 1 or 2 in severity and no Grade 4 events were reported (**Table 2**)
- No serious^ AEs of lymphopenia or neutropenia were reported
- As of the cut-off date, majority of the lymphopenia (14/16) and neutropenia (14/16) cases recovered while on ofatumumab
- Most patients in whom lymphopenia or neutropenia was reported continued treatment with ofatumumab; 2 patients with lymphopenia interrupted their treatment; no patient discontinued ofatumumab

*serious adverse event is defined as any adverse event appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:
- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Table 2. Severity and outcomes of lymphopenia and neutropenia AEs

	Overall safety population (N=1969)	
	Lymphopenia	Neutropenia
Number of patients with at least one AE - n (%) [E], IR (95% CI) per 100 PYs	16 (0.8) [18] 0.31 (0.19, 0.51)	16 (0.8) [19] 0.31 (0.19, 0.51)
Severity - n (%) [E]		
Grade 1	4 (0.2) [5]	5 (0.3) [8]
Grade 2	11 (0.6) [12]	7 (0.4) [7]
Grade 3	1 (0.1) [1]	4 (0.2) [4]
Outcome - n (%) [E]		
Recovered/resolved	14 (0.7) [16]	14 (0.7) [17]
Recovered/resolved with sequelae	0	0
Recovering/resolving	1 (0.1) [1]	0
Not recovered/resolved	1 (0.1) [1]	2 (0.1) [2]

AEs with a start date on or after the first dose of ofatumumab, up to and including last dose + 100 days are included. A patient with multiple AEs is counted only once in the "at least one AE" row. A patient with multiple events is counted only once under the maximum severity and most severe outcome.
AEs, adverse events; n, number of patients with observed event; E, number of events; PYs, patient-years.

Serious infections observed with low lymphocyte and neutrophil levels in the overall safety population

- The incidence rate (95% CI) of serious infections was 1.53 (1.23, 1.91)
- Only 5/352 patients with lymphocytes levels <LLN (vs 57/1614 ≥LLN) and 1/267 patient with neutrophil levels <LLN (vs 64/1699 ≥LLN) had serious infections in the period 1 month prior to 1 month after detection of drop in lymphocytes or neutrophils <LLN (**Table 3**)
  - Of the 5 patients with serious infections with lymphocyte levels <LLN, 4 patients had only one episode of drop in levels below LLN and 2 patients had a grade 3 event; all patients recovered during ofatumumab treatment
  - The one patient with a Grade 2 event with neutrophil levels <LLN experienced the drop in level only once and recovered during ofatumumab treatment
- No apparent association was observed between low lymphocyte and neutrophil levels and risk of serious infections up to 4 years of ofatumumab treatment

Table 3. Serious infections within 1 month prior to 1 month after any detection of drop in lymphocytes or neutrophils below LLN

	Lymphocytes		Neutrophils	
	<LLN (N=352)	≥LLN (N=1614)	<LLN (N=267)	≥LLN (N=1699)
	n; IR (95% CI)	n; IR (95% CI)	n; IR (95% CI)	n; IR (95% CI)
Patients with serious infections (PT)	5; 2.90 (1.21, 6.96)	57; 1.38 (1.07, 1.79)	1; 0.94 (0.13, 6.71)	64; 1.49 (1.16, 1.90)
Gastroenteritis	0	2; 0.05 (0.01, 0.19)	1; 0.94 (0.13, 6.71)	2; 0.05 (0.01, 0.18)
Appendicitis	1; 0.58 (0.08, 4.09)	11; 0.26 (0.15, 0.48)	0	9; 0.21 (0.11, 0.40)
UTI	1; 0.58 (0.08, 4.10)	4; 0.10 (0.04, 0.25)	0	6; 0.14 (0.06, 0.30)
Escherichia urinary tract infection	1; 0.58 (0.08, 4.09)	0	NA	NA
Kidney infection	1; 0.58 (0.08, 4.09)	1; 0.02 (0.0; 0.17)	NA	NA
Neutropenic sepsis[a]	1; 0.58 (0.08, 4.09)	0	NA	NA
Upper respiratory tract infection	1; 0.58 (0.08, 4.09)	0	NA	NA

[a]An event of neutropenic sepsis was diagnosed with no information on blood culture and recovered in two days without granulocyte colony-stimulating factor treatment while continuing on ofatumumab and with no recurrences later.
LLN (10^9/L): lymphocytes, 0.91; neutrophils, 1.96
MedDRA Version 24.1 has been used for the reporting of serious adverse events. A patient with multiple serious adverse events within a risk name is counted once in the total row. All the terms reported are within primary system organ class "Infections and Infestations".
CI, confidence interval; IR, incidence rate; LLN, lower limit of normal; NA, not applicable; N, number of patients in each group; n, number of patients with observed outcome; PT, preferred term; UTI urinary tract infection.

Conclusions

- With up to 4 years of ofatumumab treatment, mean lymphocyte and neutrophil levels remained stable and well above the LLN; majority of the drops (below LLN) occurred randomly and were not persistent
- Incidences of lymphopenia and neutropenia were comparable with core study data and remained low; no serious cases were reported
- Overall incidence of serious infections was low with no apparent association with decreased lymphocyte or neutrophil counts
- Our results support the favourable benefit-risk of the ofatumumab monthly 20 mg s.c. dosing regimen with longer-term (up to 4 years) treatment in patients with RMS

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