Effect of Ofatumumab on Serum Immunoglobulin Levels and Infection Risk in Relapsing Multiple Sclerosis (RMS) Patients from the Phase 3 ASCLEPIOS I and II Trials

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Amit Bar-Or[1], Jérôme de Seze[2], Jorge Correale[3], Anne H. Cross[4], Ludwig Kappos[5], Krzysztof Selmaj[6], Heinz Wiendl[7], Cecile Kerloeguen[8], Ratnakar Pingili[9], Roseanne Sullivan[9], Ayan Das Gupta[10], Valentine Jehl[8], Dieter A. Häring[8], Martin Merschhemke[8], Stephen L. Hauser[11]

[1]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]University Hospital of Strasbourg, Strasbourg, France; [3]Institute for Neurological Research Dr. Raul Carrea, Buenos Aires, Argentina; [4]Washington University School of Medicine, Saint Louis, MO, USA; [5]Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [6]Center for Neurology, Lodz, Poland; [7]University of Münster, Münster, Germany; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [11]Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA

Background

- Ofatumumab, the first fully human anti-CD20 monoclonal antibody[1] with a 20 mg subcutaneous (s.c.) monthly dosing regimen, demonstrated superior efficacy and a favorable safety profile versus teriflunomide 14 mg oral once daily in relapsing multiple sclerosis (RMS) patients in the Phase 3 ASCLEPIOS I and II trials[2]
  - No unexpected safety signals and no imbalance in the rates of infection (including serious infection) or malignancy were observed versus teriflunomide[2]
  - Adverse events (AEs) incidence was comparable between the ofatumumab (83.6%) and teriflunomide (84.2%) treatment groups, with majority of the AEs (>90%) being of mild-to-moderate severity[2]
- Exposure-dependent reduction in immunoglobulin M (IgM) and immunoglobulin G (IgG) levels in blood can occur in patients treated with B cell depleting therapies (secondary antibody deficiency)[3–5]
  - Increased risk of infections has been observed with low immunoglobulin levels in blood[4,6]

Objective

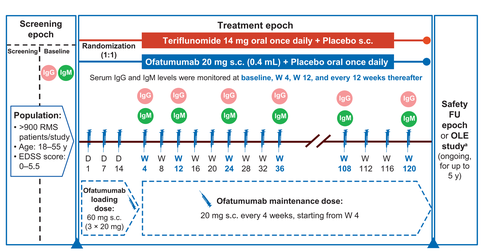
- To assess serum IgM and IgG levels and evaluate their associations with risk of infections in RMS patients treated with ofatumumab in the ASCLEPIOS I and II trials

Methods

Study design

- ASCLEPIOS I and II were double-blind, double-dummy, active comparator-controlled, parallel-group, multicenter, adaptive and flexible duration trials (maximum duration of up to 30 months: average follow-up 18 months; **Figure 1**)

Figure 1. ASCLEPIOS I/II study design and IgM/IgG assessments



[a]OLE study (up to 5 y) via a separate protocol. Patients who complete the Treatment epoch while on study drug may be eligible to participate. The Safety FU epoch is included to ensure all patients not entering the Extension can have at least 9 months FU after the last dose of the study drug.

[b]The EOS was projected based on a prospectively planned analysis of blinded data to provide 90% power for the primary endpoint, and 90% and 80% power for 3- and 6-month confirmed disability worsening, respectively. EOS was defined by the amount of statistical information collected in the trial (relapses and disability events), instead of relying on a fixed time after the last patient has been randomized.

D, day; EDSS, Expanded Disability Status Scale; EOS, end of study; FU, follow-up; Ig, immunoglobulin; RMS, relapsing multiple sclerosis; OLE, open-label extension; s.c., subcutaneous; W, week; y, year.

Study assessments

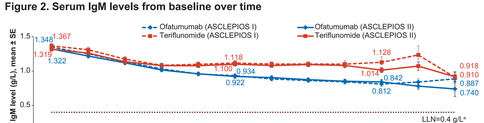
- Serum samples for IgM and IgG assessments (measured by immunoturbidometry) were collected at specified timepoints: baseline, Week (W) 4, W 12, and every 12 weeks thereafterthroughout the study (**Figure 1**)
  - Samples were stored at an ambient temperature and sent for analysis on the day of collection, or kept refrigerated (2–8°C) if there was any delay in shipping
- Parameters analyzed:
  - Changes from baseline in IgM/IgG levels up to W 120
  - Proportion of patients with low IgM/IgG levels below lower limit of normal (LLN) at W 96
    - As pre-defined in the protocol, a notable low IgM level was defined as a level that is 10% below LLN, and a notable low IgG level was defined as a level that is 20% below LLN
  - Association between low IgM/IgG levels and incidence of infections
- Safety analyses were performed on the Safety set (all patients who received at least one dose of the study medication)
- Treatment-emergent AEs (infections) were summarized descriptively by treatment group

Results

Change in serum IgM levels from baseline

- A reduction in IgM levels from baseline was observed in both treatment groups in both studies; average IgM levels remained well within the reference ranges (patients aged 16–19 years: 0.23–2.59 g/L; patients aged >19 years: 0.40–2.30 g/L; **Figure 2**)

Figure 2. Serum IgM levels from baseline over time



[a]For parameters with multiple reference ranges, the reference range for females (since majority of the population is adult female) above 19 years of age was used to display the normal limit range.

BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; N', total number of patients in each treatment arm at each time point; SE, standard error; W, week.

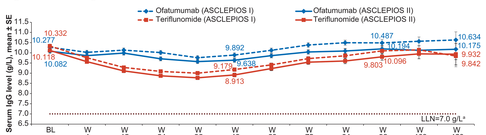
Change in serum IgG levels from baseline

- Average IgG levels remained well within the reference ranges (patients aged 16–19 years: 5.49–15.84 g/L; patients aged >19 years: 7.00–16.00 g/L)
  - A reduction from baseline in IgG levels was observed until W 36, and the IgG levels recovered thereafter in both treatment groups in both studies (**Figure 3**)
  - In ofatumumab-treated patients, the IgG levels recovered up to baseline level at W 72

Proportion of patients reaching IgM/IgG levels below LLN

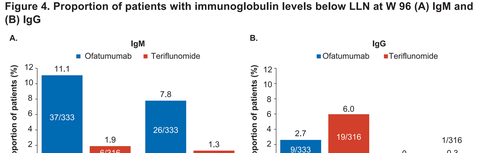
- The proportion of patients with IgM levels below LLN anytime during the post-baseline visit was higher among patients treated with ofatumumab (17.7%; 167/944) versus teriflunomide (6.6%; 62/933)
- At W 96, median IgM levels in the ASCLEPIOS I and II trials were 0.71 g/L, each in ofatumumab-treated patients, and 0.94 and 0.93 g/L, respectively, in teriflunomide-treated patients

Figure 3. Serum IgG levels from baseline over time



- At W 96, a higher proportion of patients in the ofatumumab group had IgM levels below LLN as well as 10% below LLN, compared with the patients in the teriflunomide group (**Figure 4A**)
- The proportion of patients with IgG levels below LLN anytime during the post-baseline visit was lower among patients treated with ofatumumab (14.2%; 134/944) versus teriflunomide (22.9%; 214/934)
  - No patients reached IgG levels 50% below LLN (hypogammaglobulinemia[7]) with either ofatumumab or teriflunomide at least once anytime during the post-baseline visits
- At W 96, median IgG levels in the ASCLEPIOS I and II trials were 10.33 and 9.87 g/L, in ofatumumab-treated patients, and 10.07 and 9.51 g/L, respectively, in teriflunomide-treated patients
- At W 96, a lower proportion of patients in the ofatumumab group had IgG levels below LLN compared with patients in the teriflunomide group (**Figure 4B**)
  - No patients in ofatumumab group reached IgG levels 20% below LLN compared with 0.3% of patients in the teriflunomide group

Figure 4. Proportion of patients with immunoglobulin levels below LLN at W 96 (A) IgM and (B) IgG



A notable low IgM level was defined as a level that is 10% below LLN, and a notable low IgG level was defined as a level that is 20% below LLN.

Ig, immunoglobulin; LLN, lower limit of normal

Infections observed after the first drop in IgM levels below LLN

- The proportion of patients who experienced infections after the first drop in IgM levels below LLN was comparable between the ofatumumab (29.9%) and teriflunomide (33.9%) groups (**Table 1**)
  - In ofatumumab-treated patients, all infections were Grade 1/2, except four Grade 3 events (vulvovaginitis, n=1; urinary tract infection, n=2; and influenza, n=1). In teriflunomide-treated patients, all infections were Grade 1/2
  - After the first drop in IgG levels below LLN, 3 patients treated with ofatumumab experienced serious infections (upper respiratory tract infection, urinary tract infection/kidney infection, and pneumonia) compared with 2 patients in the teriflunomide group (pneumonia influenza and osteomyelitis). All infections were resolved
- Of the 20 ofatumumab-treated patients with IgM levels 50% below LLN, four patients experienced infections after the first drop in IgM 50% below LLN: most of them were Grade 1/2, except one Grade 3 infection (urinary tract infection [serious infection]). All infections were resolved. One patient on teriflunomide who experienced nasopharyngitis had not recovered at the time of last follow-up

Table 1. Infections observed in patients[a] after the first drop in IgM levels below LLN compared to infections in the overall ASCLEPIOS I and II pooled population

Preferred term	Patients with infections after first drop in IgM levels below LLN		ASCLEPIOS I and II pooled population	
	Ofatumumab N'=167, n (%)	Teriflunomide N'=62, n (%)	Ofatumumab N=946, n (%)	Teriflunomide N=936, n (%)
Patients with at least one infection	50 (29.9)	21 (33.9)	488 (51.6)	493 (52.7)
Nasopharyngitis	12 (7.2)	6 (9.7)	170 (18.0)	156 (16.7)
Upper respiratory tract infection	10 (6.0)	9 (14.5)	97 (10.3)	120 (12.8)
Urinary tract infection	11 (6.6)	2 (3.2)	97 (10.3)	78 (8.3)
Gastroenteritis	5 (3.0)	1 (1.6)	27 (2.9)	22 (2.4)
Pharyngitis	5 (3.0)	0 (0)	28 (3.0)	19 (2.0)
Patients with at least one serious infection	2 (1.2)	0 (0)	24 (2.5)	17 (1.8)

[a]For parameters with multiple reference ranges, the reference range for females (since majority of the population is adult female) above 19 years of age was used to display the normal limit range.

A patient with multiple infections within a high level term was counted only once in the total row. A patient with multiple occurrences of an infection under one treatment was counted only once in the infection category for that treatment.

[b]Patients with ≥2% infections after the first drop in IgM levels below LLN in the ofatumumab group.

LLN=0.4 g/L for IgM. For parameters with multiple reference ranges, the reference range for females (since majority of the population is adult female) above 19 years of age was used to display the normal limit range.

Ig, immunoglobulin; LLN, lower limit of normal; N', total number of patients with IgM levels below LLN in each treatment arm; N, number of patients in ASCLEPIOS I and II pooled population.

Infections observed after the first drop in IgG levels below LLN

- The proportion of patients who experienced infections after the first drop in IgG levels below LLN was numerically higher for ofatumumab (45.5%) versus teriflunomide (36.4%)
  - All infections were Grade 1/2, except one event in the ofatumumab group (bilateral pneumonia, Grade 3) and two events in the teriflunomide group (pneumonia influenza and osteomyelitis, Grade 3)

Table 2. Infections observed in patients[a] after the first drop in IgG levels below LLN compared to infections in the overall ASCLEPIOS I and II pooled population

Preferred term	Patients with infections after first drop in IgG levels below LLN		ASCLEPIOS I and II pooled population	
	Ofatumumab N'=134, n (%)	Teriflunomide N'=214, n (%)	Ofatumumab N=946, n (%)	Teriflunomide N=936, n (%)
Patients with at least one infection	61 (45.5)	78 (36.4)	488 (51.6)	493 (52.7)
Nasopharyngitis	21 (15.7)	23 (10.7)	170 (18.0)	156 (16.7)
Upper respiratory tract infection	15 (11.2)	24 (11.2)	97 (10.3)	120 (12.8)
Urinary tract infection	11 (8.2)	9 (4.2)	97 (10.3)	78 (8.3)
Influenza	7 (5.2)	6 (2.8)	62 (6.6)	59 (6.3)
Sinusitis	6 (4.5)	4 (1.9)	30 (3.2)	31 (3.3)
Bronchitis	4 (3.0)	6 (2.8)	24 (2.5)	33 (3.5)
Gastroenteritis	4 (3.0)	3 (1.4)	27 (2.9)	22 (2.4)
Rhinitis	3 (2.2)	4 (1.9)	25 (2.6)	22 (2.4)
Patients with at least one serious infection	3 (2.2)	2 (0.9)	24 (2.5)	17 (1.8)

A patient with multiple infections within a high level term was counted only once in the total row. A patient with multiple occurrences of an infection under one treatment was counted only once in the infection category for that treatment.

[a]Patients with ≥2% infections after the first drop in IgG levels below LLN in the ofatumumab group.

LLN=7.0 g/L for IgG. For parameters with multiple reference ranges, the reference range for females (since majority of the population is adult female) above 19 years of age was used to display the normal limit range.

Ig, immunoglobulin; LLN, lower limit of normal; N', total number of patients with IgG levels below LLN in each treatment arm; N, number of patients in ASCLEPIOS I and II pooled population.

- Risk of serious infections was low in patients with IgM/IgG levels below LLN in both treatment groups (ofatumumab vs. teriflunomide: 1.2% vs. 0% for IgM; 2.2% vs. 0.9% for IgG) (**Tables 1** and **2**)
  - After the first drop in IgM levels below LLN, 2 patients treated with ofatumumab experienced serious infections (influenza and urinary tract infection). No patient from the teriflunomide group experienced serious infections

Conclusions

- Average serum IgM/IgG levels remained well within the reference ranges over time
  - A reduction in serum IgM levels was observed over time, but for the majority of the patients the levels remained above LLN
  - There was no decrease in mean IgG levels over time compared to baseline
- There was no apparent association of decreased immunoglobulin levels with an increased risk of serious/non-serious infections in RMS patients treated with ofatumumab
  - Nasopharyngitis, upper respiratory tract infections, and urinary tract infections were the most common infections after the first drop in IgM/IgG levels below LLN, which is consistent with the ASCLEPIOS pooled population
  - Overall incidence of Grade 3 or serious infections remained low after the first drop in IgM/IgG levels below LLN in both treatment groups; no opportunistic infections were observed
  - Most of the infections reported were non-serious in nature and were mild-to-moderate in severity; most cases were resolved while continuing ofatumumab therapy

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