Serum immunoglobulin levels and infection risk in the Phase 3 trials of ofatumumab in relapsing multiple sclerosis

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Background and objective

- Ofatumumab, an FDA-approved fully human anti-CD20 monoclonal antibody[1], with a 20 mg s.c. monthly dosing regimen, is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults[2]
- Ofatumumab demonstrated superior efficacy versus teriflunomide 14 mg oral once daily and a favorable safety profile in RMS patients in the Phase 3 ASCLEPIOS I/II trials[3]
  - No unexpected safety signals or imbalance in the rates of infection (including serious infections) or malignancies were observed[3]
  - The incidence of adverse events (AEs) was comparable between the ofatumumab (83.6%) and teriflunomide (84.2%) treatment groups, with mild to moderate severity for the majority of AEs (>90%)[3]
- Reductions in serum IgM/IgG and an associated increased risk of infections has been reported with other anti-CD20 therapies[4-7]

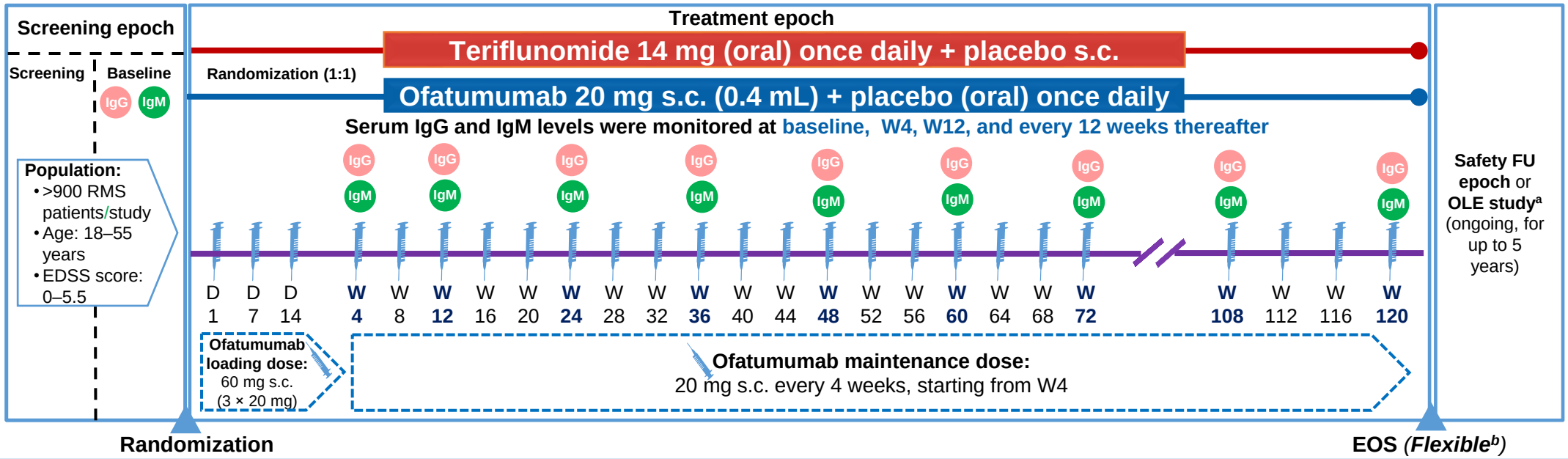
Objective	**To assess the effect of ofatumumab on serum immunoglobulin levels and evaluate potential association between decreased IgM/IgG levels and risk of infections in clinical trials**

AE, adverse event; Ig, immunoglobulin; RMS, relapsing multiple sclerosis; s.c, subcutaneous

1. Bar-Or A, et al. Neurology. 2018;90(20):e1805–e1814. 2. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed Aug 24, 2020). 3. Hauser SL, et al. Presented at ECTRIMS 2019;OP336. 3. Kim SH, et al. JAMA Neurol. 2013;70:1110–7. 4. Tallantyre EC, et al. J Neurol. 2018;265:1115–22. 5. Derfuss T, et al. Mult Scler. 2019;25(S2):3–130 (Presented at ECTRIMS 2019: OP65). 6. Furst DE. Semin Arthritis Rheum. 2009;39:18–29.

Study design and assessments

ASCLEPIOS I and II were double-blind, double-dummy, parallel-group, adaptive and flexible duration trials



Assessments

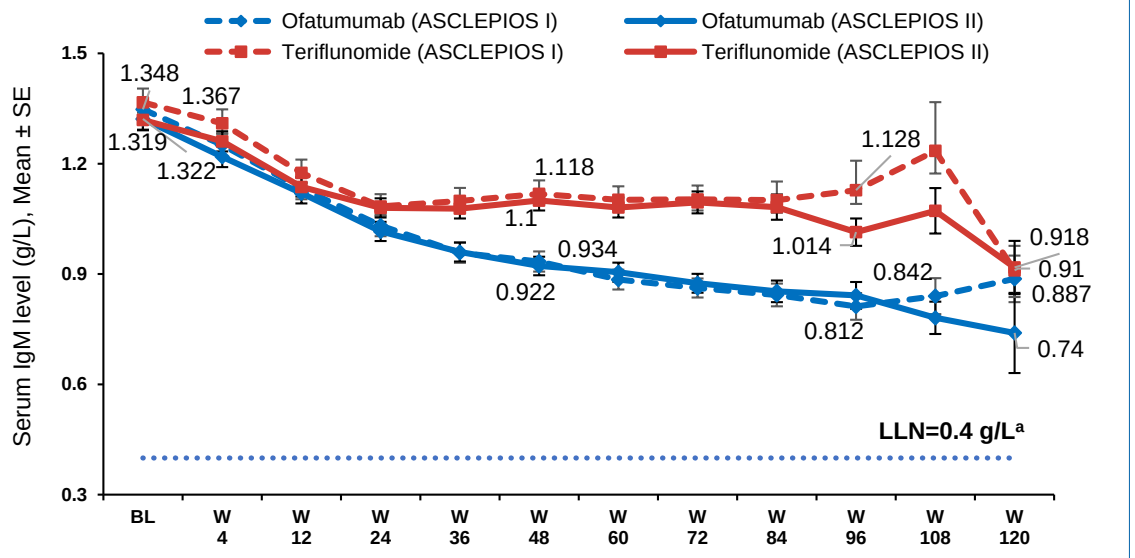
- The proportion of patients with IgM/IgG levels below the lower limit of normal (<LLN [g/L]: IgM, 0.4; IgG, 7.0) and the association of infections occurring in conjunction with a decrease in either IgM or IgG levels <LLN 1 month prior and until 1 month after detection of any series of decrease in IgM or IgG levels were analyzed and compared with infections reported in patients who maintained normal immunoglobulin levels (≥LLN)
- Infections in conjunction with IgM/IgG <LLN and lymphopenia and/or neutropenia[c] on the same visit were also analyzed

[a]OLE study (up to 5 years) via a separate protocol. Patients who complete the treatment epoch while on the 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 of 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. 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. [c]Defined as neutrop and lymphocyte blood count decreased.

D, day; EOS, end of study; FU, follow-up; Ig, immunoglobulin; LLN, lower limit of normal; OLE, open label extension; RMS, relapsing multiple sclerosis; s.c., subcutaneous; W, week

Change in serum IgM and IgG levels observed from baseline over time

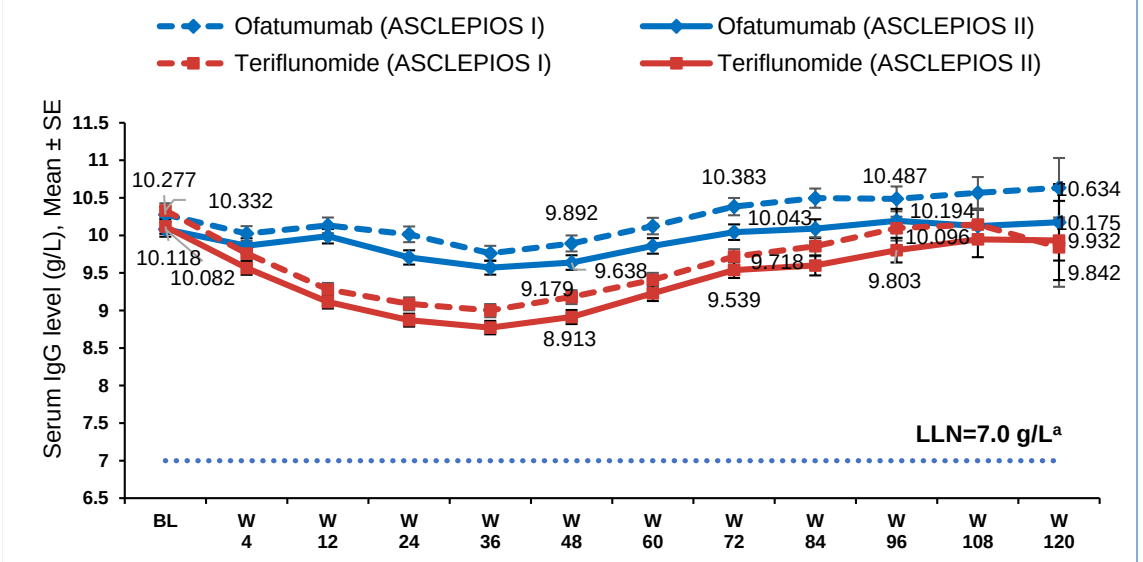
IgM



Reference ranges: Patients aged 16–19 years: 0.23–2.59 g/L; >19 years: 0.40–2.30 g/L

- A reduction in mean serum IgM levels from baseline was observed in both treatment groups in both studies, a greater reduction was observed with ofatumumab versus teriflunomide
- Overall, mean serum IgM levels remained well above the lower limit normal over time

IgG



Reference ranges: Patients aged 16–19 years: 5.49–15.84 g/L; >19 years: 7.00–16.00 g/L

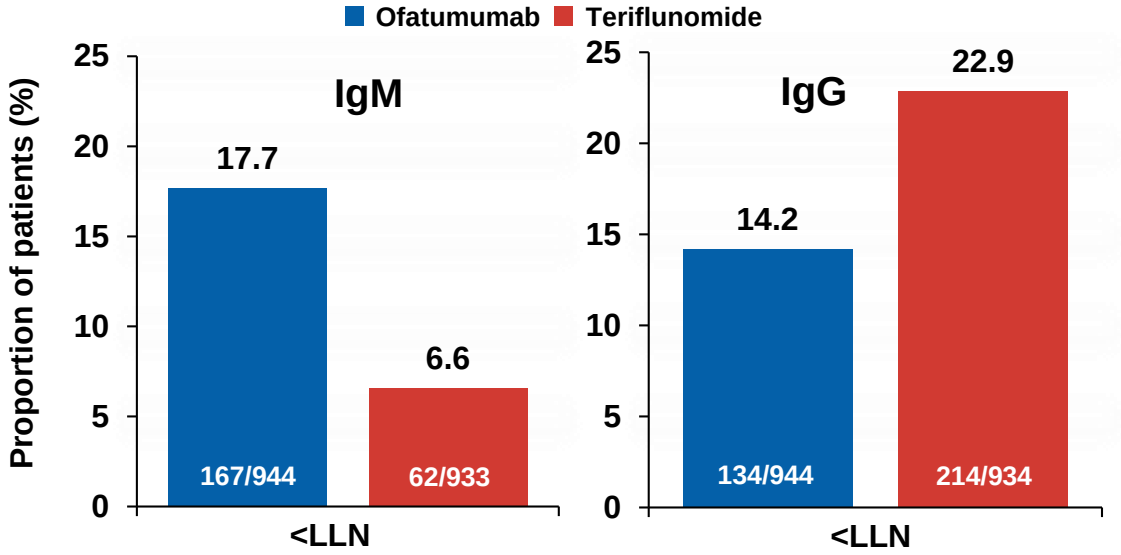
- No reduction in the mean serum IgG was observed in the ofatumumab-treated patients over time
- A transient reduction in IgG levels from baseline was observed until Week 36, which recovered to baseline value by Week 72 in the ofatumumab-treated patients; a greater reduction of mean serum IgG was observed with teriflunomide

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

BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; SE, standard error; W, Week

Proportions of patients with IgM and IgG levels below the LLN at any time during post-baseline visits

Proportion of patients with IgM/IgG <LLN at any time post-baseline



IgM <LLN at baseline (n/M; %): Ofatumumab (1/945; 0.1%) and teriflunomide (1/934; 0.1%)
IgG <LLN at baseline (n/M; %): Ofatumumab (5/945; 0.5%) and teriflunomide (7/934; 0.7%)

Treatment interruptions/discontinuations in ofatumumab-treated patients due to decline in IgM/IgG <LLN

IgM <LLN (n=167)	IgG <LLN (n=134)
• 42 patients required temporary interruption, as stipulated by the protocol (10% <LLN)[a] • 30 patients discontinued treatment	• 2 patients required temporary interruption, as stipulated by the protocol (20% <LLN)[a] • 4 patients discontinued treatment (2 patients with both IgG and IgM <LLN)

- Majority of the patients continued to receive treatment with ofatumumab and did not discontinue treatment

At any time post-baseline, a higher proportion of patients on ofatumumab had IgM <LLN, while a lower proportion had IgG <LLN, versus patients on teriflunomide

Treatment discontinuations in patients with low IgM/IgG were generally not due to infections but rather triggered by protocol stipulated threshold i.e., treatment continued until immunoglobulin levels reach LLN[a]

[a]A notable low IgM level was defined as a level that is 10% below the LLN; A notable low IgG level was defined as a level that is 20% below the LLN

Ig, immunoglobulin; LLN, lower limit of normal; M, total number of patients with a non-missing value for baseline; n, the number of patients who are at the corresponding category

Association of infections with IgM/IgG decrease in ofatumumab-treated patients

Patients with at least one infection within 1 month prior and until 1 month after the drop in IgM/IgG levels below the LLN

	Pooled ofatumumab		IgM				IgG			
	N=946		<LLN (N=167[a])		≥LLN (N=777[b])		<LLN (N=134[a])		≥LLN (N=810[b])	
	n (%)	IR	n (%)	IR[c]	n (%)	IR[c]	n (%)	IR[c]	n (%)	IR[c]
Patients with at least one infection	**488 (51.6)**	**51.14**	**52 (31.1)**	**69.61**	**400 (51.5)**	**50.24**	**37 (27.6)**	**80.30**	**410 (50.6)**	**49.54**
Patients with at least one serious infection	24 (2.5)	1.44	2 (1.2)	2.02	18 (2.3)	1.39	3 (2.2)	4.77	21 (2.6)	1.58
Upper respiratory tract infection (PT)	1 (0.1)	0.06	1 (0.6)	1.01	0	0	1 (0.7)	1.56	0	0
Urinary tract infection (PT)	3 (0.3)	0.18	1 (0.6)	1.01	2 (0.3)	0.15	0	0	3 (0.4)	0.22
Escherichia urinary tract infection (PT)	1 (0.1)	0.06	0	0	1 (0.1)	0.08	1 (0.7)	1.58	0	0
Kidney infection (PT)	1 (0.1)	0.06	0	0	1 (0.1)	0.08	1 (0.7)	1.58	0	0
Pneumonia (PT)	1 (0.1)	0.06	0	0	1 (0.1)	0.08	1 (0.7)	1.56	0	0

- **No association was observed with decreased immunoglobulins levels and increased risk of serious/non-serious infections in ofatumumab-treated patients**

[a]Number of patients with IgM/IgG <LLN at least once at any time during the post baseline visits; [b]Number of patients with no occurrence of IgM/IgG <LLN at least once at any time during the post baseline visit; [c]IR per 100 PY estimated via Poisson regression model with only treatment as the factor and with the log-link and natural logarithm of time as the offset variable.
Ig, immunoglobulin; IR, incidence rate; LLN, lower limit of normal; PT, preferred-term; PY, patient-year

Summary of infections with IgM/IgG decrease in ofatumumab-treated patients

Patients with at least one infection within 1 month prior and until 1 month after the drop in IgM/IgG levels below the LLN

	IgM		IgG	
	<LLN (N=167[a])	≥LLN (N=777[b])	<LLN (N=134[a])	≥LLN (N=810[b])
	n (%)	n (%)	n (%)	n (%)
Patients with at least one infection	52 (31.1)	400 (51.5)	37 (27.6)	410 (50.6)
Patients with concomitant treatment received for infections	44 (26.3)	359 (46.2)	31 (23.1)	365 (45.1)
Patients with at least one infection by Grade[c]				
Grade 1	22 (13.2)	202 (26.0)	18 (13.4)	204 (25.2)
Grade 2	27 (16.2)	183 (23.6)	18 (13.4)	186 (23.0)
Grade 3	3 (1.8)	14 (1.8)	1 (0.7)	18 (2.2)
Grade 4	0	1 (0.1)	0	2 (0.2)
Patients with at least one infection by action taken[d]				
Drug withdrawn	2 (1.2)	1 (0.1)	1 (0.7)	2 (0.2)
Drug interrupted	3 (1.8)	16 (2.1)	3 (2.2)	17 (2.1)

- **Most of the infections reported were non-serious and were mild to moderate in severity; most cases were resolved while continuing ofatumumab therapy**

[a]Number of patients with IgM/IgG <LLN at least once at any time during the post baseline visits; [b]Number of patients with no occurrence of IgM/IgG <LLN at least once at any time during the post baseline visit; [c]A patient with multiple events is counted only once under the most severe grade with the following hierarchy: Grade 4, Grade 3, Grade 2, Grade 1; [d]A patient with multiple events is counted only once under the most severe action taken with the following hierarchy: Drug withdrawn, Drug interrupted.
Ig, immunoglobulin; LLN, lower limit of normal

Association of infections with low IgM/IgG and concurrent lymphopenia and/or neutropenia in ofatumumab-treated patients

Patients with at least one infection within 1 month prior and until 1 month after the drop in IgM/IgG levels below the LLN

- Eleven patients (11/167; 6.6%) had concurrent IgM <LLN and lymphopenia and/or neutropenia. Of these, 1 patient reported an infection (upper respiratory tract infection)
- Twenty patients (20/134; 14.9%) had concurrent IgG <LLN and lymphopenia and/or neutropenia. Of these, 7 patients reported infections
  - Upper respiratory tract infections (n=2)
  - Nasopharyngitis (n=2)
  - Urinary tract infections (n=2)
  - Alveolar osteitis (n=1)
- No association was observed between decreased immunoglobulin levels and infections in conjunction with lymphopenia and/or neutropenia in patients treated with ofatumumab
- None of the infections were serious and most were mild to moderate in severity

Ig, immunoglobulin; LLN, lower limit of normal; n, number of patients

Conclusions

- No association was observed between a decrease in immunoglobulin levels and the incidence of serious/non-serious infections in ofatumumab-treated patients who experienced infections within 1 month prior and until 1 month after a reduction in immunoglobulin levels below the lower limit of normal
  - Most of the infections reported were non-serious in nature and were mild to moderate in severity; most cases were resolved while patients were continuing ofatumumab therapy
- No association was observed between decreased immunoglobulin levels and infections in conjunction with lymphopenia and/or neutropenia was observed in ofatumumab-treated RMS patients

Ig, immunoglobulin; RMS, relapsing multiple sclerosis

Thank you