Effect of Ofatumumab on Serum Immunoglobulin Levels and Infection Risk in Patients With Relapsing Multiple Sclerosis Over 3.5 Years

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Introduction

- Lower serum immunoglobulin (Ig) levels are generally associated with infections; reduced Ig levels is known to occur with anti-CD20 treatment in multiple sclerosis (MS) patients and have been linked to an apparent increased risk of infection[1-8]
- In the ofatumumab ASCLEPIOS Phase 3 trials, the rate of serious infections was low, and no association was observed between decreased Ig levels and the risk of serious infections for up to 96 weeks[9]

Objective

- To assess the effect of ofatumumab on serum IgG/IgM levels over ~3.5 years (168 weeks) and evaluate the risk of serious infections associated with a decrease in IgG/IgM during the core (ASCLEPIOS I/II, APLIOS or APOLITOS) and open-label extension (ALITHIOS) studies

Methods

Study Design and Assessments

- Serum IgG/IgM levels were monitored during the core and open-label extension study periods
- Change in IgG/IgM levels from baseline up to 168 weeks was analysed in the overall, long-term (continuous ofatumumab in core+extension) and switch (teriflunomide core/ofatumumab extension) groups
- Mean IgG/IgM levels were analysed by baseline quartiles in the long-term treatment group
- Proportion of patients with IgG/IgM less than lower limit of normal (<LLN: IgM, 0.4 g/L; IgG, 5.65 g/L) at any time during the post-baseline visits was assessed
- Association of serious infections reported for patients in conjunction with low IgG/IgM levels <LLN during 1 month prior/after any detection of the drop in the levels were analysed and compared with serious infections reported in patients who maintained normal Ig levels (≥LLN)

Results

- As of 29 Jan 2021, median time at risk (treatment-emergent period of a patient in the study) was 21.0 (range: 0 to 51.8) months in the overall and 35.5 months in long-term group; total 4238.5 patient-years
- Change in IgG/IgM levels was analysed in the overall (N=1969), long-term (N=1292) and switch (N=677) groups

Change in IgG levels over 3.5 years

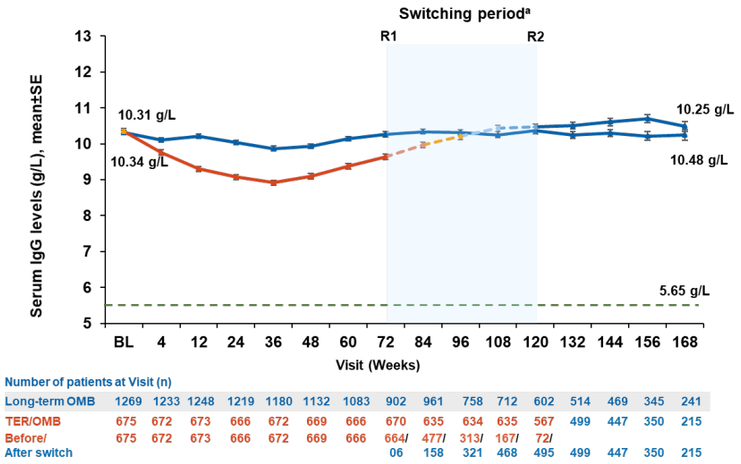
- The mean serum IgG remained stable with up to 3.5 years of ofatumumab treatment **(Figure 1A)**
- Ofatumumab was associated with a transient drop in IgG levels through Week 48, which completely recovered and was maintained at later time points
- Patients did not show any decline after switching from teriflunomide and followed the same trajectory as of long-term ofatumumab group
- Treatment interruptions* and discontinuations were observed in 0.1% and 0.2% of patients respectively

Change in IgM levels over 3.5 years

- Average IgM levels remained well within the reference ranges over time **(Figure 1B)**
- Most of the reduction from baseline in IgM levels was observed at Week 48 (absolute mean, 0.93 g/L; % change, −31.8%), which stabilised thereafter (Week 168: absolute mean, 0.71 g/L; % change, −46%)
- Treatment interruptions* and discontinuations were observed in 9.1% and 3.3% of patients respectively

*As per the study protocol, study treatment interruption was mandated based on notably low IgG/IgM values. A notably low level for IgG was defined as a level 20% below the LLN and for IgM as a level 10% below the LLN

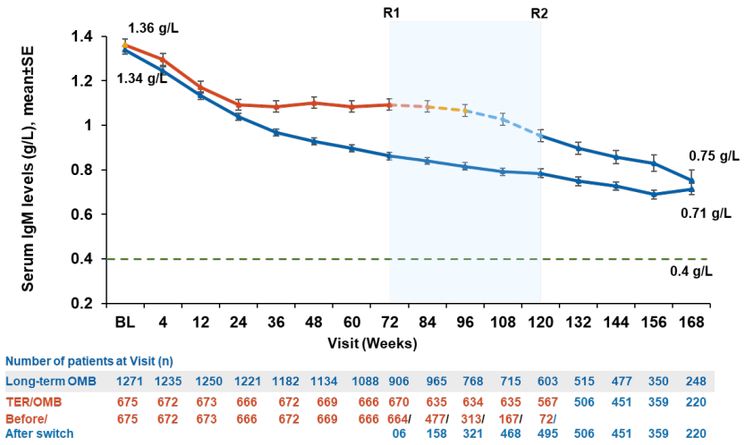
Figure 1A. Serum IgG levels from baseline over time



Number of patients at Visit (n)

Long-term OMB	1269	1233	1248	1219	1180	1132	1083	902	961	758	712	602	514	469	345	241
TER/OMB	675	672	673	666	672	669	666	670	635	634	635	567	499	447	350	215
Before/ After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 321	167/ 468	72/ 495	499	447	350	215

Figure 1B. Serum IgM levels from baseline over time



Number of patients at Visit (n)

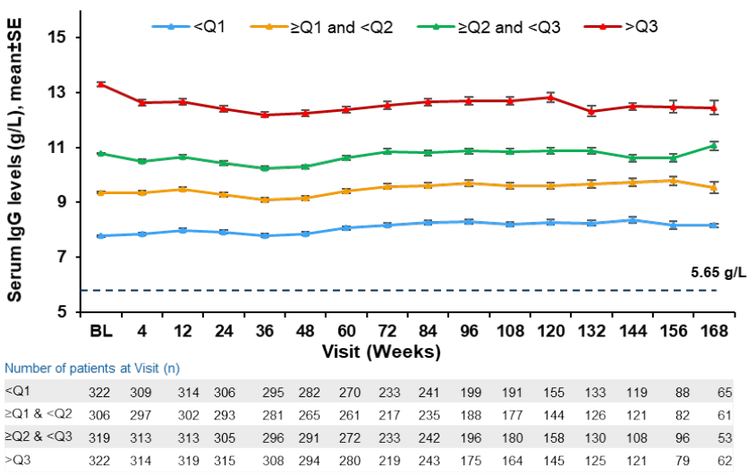
Long-term OMB	1271	1235	1250	1221	1182	1134	1088	906	965	768	715	603	515	477	350	248
TER/OMB	675	672	673	666	672	669	666	670	635	634	635	567	506	451	359	220
Before/ After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 321	167/ 468	72/ 495	506	451	359	220

Long-term OMB, N=1292; TER/OMB, N=677; 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); [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; The duration of the study is variable per subject. BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; SE, standard error; TER/OMB, Switched from teriflunomide to ofatumumab.

IgG/IgM levels by baseline quartiles in the long-term group

- IgG levels remained similar to the baseline values in all quartiles throughout the treatment period **(Figure 2A)**
- IgM levels decreased over time; the mean values remained above LLN with the least reduction observed for the lowest quartile group (<0.81 g/L) **(Figure 2B)**

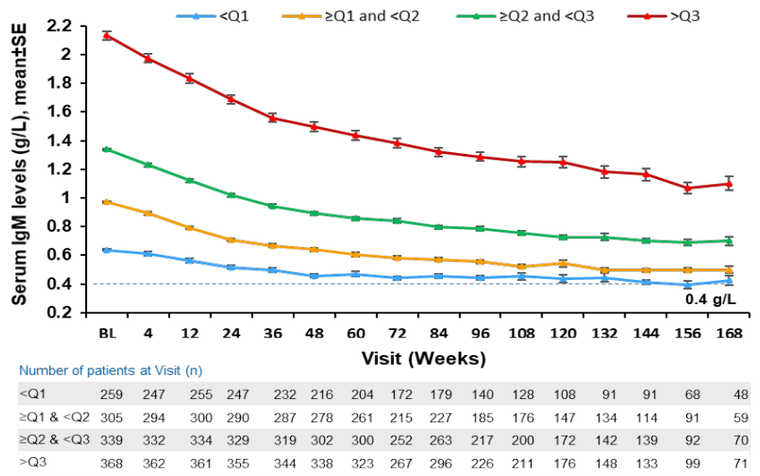
Figure 2A. Serum IgG levels by baseline quartiles[a] in the long-term ofatumumab group



Number of patients at Visit (n)

<Q1	322	309	314	306	295	282	270	233	241	199	191	155	133	119	88	65
≥Q1 & <Q2	306	297	302	293	281	265	261	217	235	188	177	144	126	121	82	61
≥Q2 & <Q3	319	313	313	305	296	291	272	233	242	196	180	158	130	108	96	53
>Q3	322	314	319	315	308	294	280	219	243	175	164	145	125	121	79	62

Figure 2B. Serum IgM levels by baseline quartiles[a] in the long-term ofatumumab group



Number of patients at Visit (n)

<Q1	259	247	255	247	232	216	204	172	179	140	128	108	91	91	68	48
≥Q1 & <Q2	305	294	300	290	287	278	261	215	227	185	176	147	134	114	91	59
≥Q2 & <Q3	339	332	334	329	319	302	300	252	263	217	200	172	142	139	92	70
>Q3	368	362	361	355	344	338	323	267	296	226	211	176	148	133	99	71

Long-term OMB, N=1292; For all pooled analyses, a fixed value of LLN (using ALITHIOS study reference) was used: IgG: 5.65 g/L and IgM: 0.4 g/L; [a]Quartiles for IgG (g/L) Q1: 8.57, Q2: 10.07 and Q3: 11.51; [b]For IgM (g/L) Q1: 0.81, Q2: 1.14, and Q3: 1.57; The duration of the study is variable per subject. BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; Q, quartile; SE, standard error.

Serious infections observed with low IgG/IgM in overall ofatumumab-treated patients

- The proportion of patients who were <LLN at any time post-baseline was 1.5% (30/1969) for IgG and 23.1% (454/1969) for IgM
- The overall incidence of serious infections was low over 3.5 years (2.9%; IR, 1.39) **(Table 1)**
- No apparent association was observed between low IgG/IgM levels and risk of serious infections after 3.5 years of ofatumumab treatment; none of these patients with a serious infection suffered a recurrence
- No COVID-19 infections were observed related to IgG/IgM <LLN during this period

Table 1. Patients with ≥1 serious infection within 1 month prior/after any detection of drop in IgG/IgM <LLN

	IgG		IgM		Overall
	<LLN (N=30[a])	≥LLN (N=1936[b])	<LLN (N=454[a])	≥LLN (N=1512[b])	N=1969
	n (%); IR[c]	n (%); IR[c]	n (%); IR[c]	n (%); IR[c]	n (%); IR[c]
Patients with ≥1 serious infection (PT)	1 (3.3); 7.02	55 (2.8); 1.34	3 (0.7); 0.80	44 (2.9); 1.38	58 (2.9); 1.39
Herpes zoster	0	1 (0.1); 0.02	1 (0.2); 0.27	0	1 (0.1); 0.02
URTI	0	1 (0.1); 0.02	1 (0.2); 0.27	0	1 (0.1); 0.02
UTI	0	6 (0.3); 0.14	1 (0.2); 0.27	3 (0.2); 0.09	6 (0.3); 0.14
Pneumonia	1 (3.3); 7.02	8 (0.4); 0.19	0	8 (0.5); 0.25	9 (0.5); 0.21

[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 a 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; URTI, upper urinary tract infection; UTI, urinary tract infection

Conclusions

- Mean IgG levels remained stable in patients treated with ofatumumab for up to 3.5 years
- A gradual decline in mean IgM levels was observed, which was more pronounced in the first year than in the subsequent time period
  - However, for the vast majority of patients, IgM levels remained well within the normal reference range
- The overall incidence of serious infections was low, and no association was observed between decreased Ig levels and the risk of serious infections
- Results from this analysis up to 3.5 years of ofatumumab treatment are consistent with 96-week ASCLEPIOS I/II Phase 3 data[10]

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