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Long-Term Effect of Ofatumumab on Serum Immunoglobulin Levels in Patients With Relapsing Multiple Sclerosis

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KEY FINDINGS & CONCLUSIONS

- This study evaluated the effect of ofatumumab (OMB) on serum immunoglobulin (Ig) levels in 1969 patients with relapsing forms of multiple sclerosis during the ASCLEPIOS I/II, APLIOS, and APOLITOS core studies and/or the ALITHIOS open-label extension study
- The serum IgG and IgM levels remained above the lower limit of normal (LLN) in the majority of patients (98.0% and 69.4%, respectively) at all assessments from the first dose of OMB for up to 5 years
- Sensitivity analyses showed that interruption/discontinuation of OMB treatment due to low IgG/IgM levels (below the LLN) did not affect the overall IgG/IgM patterns

INTRODUCTION

- Ofatumumab (OMB), a fully human anti-CD20 monoclonal antibody with a 20-mg subcutaneous monthly dosing regimen, is approved for treating relapsing multiple sclerosis (RMS) in adults[1]
- In the phase 3 ASCLEPIOS I/II trials, OMB treatment for up to 30 months had a favorable safety profile and was generally well tolerated in patients with RMS[2]
- The cumulative safety data of OMB treatment for up to 5 years have shown[3]:
  - Most patients had serum immunoglobulin (Ig) levels that remained above the lower limit of normal (LLN)
  - The mean serum IgG levels remained similar to the baseline values
  - The mean serum IgM levels decreased over time but stayed above the LLN
- Some studies with anti-CD20 therapies have shown that low IgG levels may be associated with higher risk of infections[4]

OBJECTIVE

- This study evaluated the effect of OMB on serum IgG/IgM levels for up to 5 years during the core and open-label extension (OLE) studies

METHODS

Patient Population

- The effect of OMB on IgG and IgM levels for up to 5 years (data cutoff: September 25, 2022; time on OMB: 6670.1 patient-years) was analyzed in the overall safety population (N=1969) comprising patients who received OMB in the ASCLEPIOS I/II, APOLITOS, or APLIOS core studies and/or the ALITHIOS OLE

Key Assessments

- The proportion of patients with IgG/IgM levels <LLN (LLN: IgG, 5.65 g/L; IgM, 0.4 g/L)
  - Serum IgG/IgM levels were measured at Week (W) 4, W12, and every 3 months thereafter in ASCLEPIOS; every 3 months in the first year of ALITHIOS and then every 6 months afterwards; and at W4, W12, and every 3 months thereafter in APOLITOS and APLIOS during the safety follow-up
    - Serious infections that occurred within 1 month prior and until 1 month after single or consecutive values of IgG (or IgM) <LLN were analyzed
- Sensitivity analysis was conducted to determine whether OMB interruption due to low IgG/IgM would impact overall Ig trends
  - IgG and IgM values after the first interruption due to either notably low IgM (10% <LLN) or IgG (20% <LLN) levels were imputed using the last observation carried forward
- The proportion of patients with treatment interruptions*/discontinuations due to IgG/IgM decline was analyzed

*In ASCLEPIOS I/II, the investigators were required to interrupt study treatment if IgM levels fell 10% below the LLN or if IgG levels fell 20% below the LLN. Due to a protocol change at the beginning of ALITHIOS (ie, June 3, 2021), the requirement to interrupt treatment based on a specific threshold due to low IgG/IgM was removed and was left to the discretion of the investigator

RESULTS

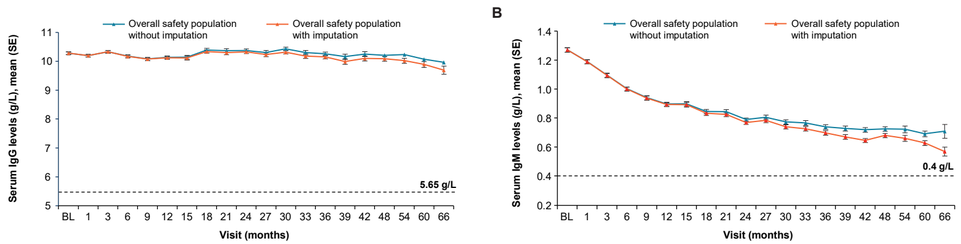
Proportion of Patients With IgG/IgM Levels <LLN

- Serum IgG levels remained above the LLN in 98.0% of patients, whereas serum IgM levels remained above the LLN in 69.4% of patients at all assessments from the first dose of OMB for up to 5 years
- Serious infections were reported in 3/40 (7.5%) patients with IgG levels <LLN (vs 99/1926 [5.1%], ≥LLN) and 10/601 (1.7%) patients with IgM levels <LLN (vs 72/1365 [5.3%], ≥LLN)
  - Serious infections in patients with IgG<LLN were pneumonia (n=1), COVID-19 pneumonia (n=1), and chronic pyelonephritis (n=1), and most frequent serious infections in patients with IgM<LLN were COVID-19 (n=4) and urinary tract infection (n=2)
- No clinically meaningful association was observed between decreased IgG/IgM levels and the risk of serious infections

Mean Serum IgG/IgM Levels With and Without Imputation

- Sensitivity analysis showed that no major difference was observed in the overall mean IgG and IgM trend after imputing IgG/IgM levels over time for patients who interrupted OMB due to either notably low IgM or IgG levels (**Figure 1A**, **1B**)

Figure 1. Serum (A) IgG and (B) IgM Levels



Number of patients at visit, n

	BL	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	48	54	60	66
Without imputation	1946	1901	1907	1828	1679	1716	1466	982	982	1364	906	1218	714	1032	530	712	711	564	515	248
With imputation	1946	1901	1907	1830	1685	1724	1502	1014	1015	1423	946	1303	782	1149	623	878	796	669	622	395

Number of patients at visit, n

	BL	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	48	54	60	66
Without imputation	1948	1903	1909	1835	1686	1719	1085	1469	986	1372	910	1225	719	1041	538	725	711	566	514	249
With imputation	1948	1903	1909	1837	1692	1727	1095	1502	1015	1428	947	1307	785	1151	625	881	796	669	622	395

BL, baseline; Ig, immunoglobulin; SE, standard error

Treatment Interruptions/Discontinuations in the Overall Safety Population

- Most patients did not interrupt and did not discontinue OMB treatment (99.8% for both) due to low IgG levels
- Overall, 96.4% of patients did not discontinue treatment and 89.7% did not interrupt treatment due to low IgM levels (**Table 1**)

Table 1. IgG-/IgM-Related Treatment Interruptions and Discontinuations in the Core, Extension, and Overall Safety Populations

		Core population (N=1292) n (%)	Extension population (N=1703) n (%)	Overall safety population (N=1969) n (%)
IgG	Either interruption or discontinuation	3 (0.2)	3 (0.2)	6 (0.3)
	Interruption*	1 (0.1)	2 (0.1)	3 (0.2)
	Discontinuation*	3 (0.2)	1 (0.1)	4 (0.2)
IgM	Either interruption or discontinuation	70 (5.4)	199 (11.7)	254 (12.9)
	Interruption*	46 (3.6)	170 (10.0)	202 (10.3)
	Discontinuation*	27 (2.1)	44 (2.6)	71 (3.6)

Ig, immunoglobulin
*Patients with interruption and discontinuation have been included in both categories

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Disclosures

Amit Bar-Or has received consulting fees from and participated as a speaker in meetings sponsored by Accure, Atara Biotherapeutics, Biogen, Bristol Myers Squibb/Celgene/Receptos, GlaxoSmithKline, Gossamer Bio, Janssen/Actelion, MedImmune, Merck/EMD Serono, Novartis, Roche/Genentech, and Sanofi-Genzyme and has received grant support from Biogen, Merck/EMD Serono, Novartis, and Roche/Genentech. **Heinz Wiendl** has received honoraria for acting as a member of scientific advisory boards for Biogen, Evgen, Genzyme, MedDay, Merck/EMD Serono, Novartis, Roche Pharma AG, and Sanofi-Aventis; has received speaker honoraria and travel support from Alexion, Biogen, Cognomed, F. Hoffmann-La Roche Ltd, Gemeinnützige Hertie-Stiftung, Genzyme, Merck/EMD Serono, Novartis, Roche Pharma AG, Teva, and WebMD Global; is a paid consultant for AbbVie, Actelion, Biogen, IGES, Johnson & Johnson, Novartis, Roche, Sanofi-Aventis, and the Swiss Multiple Sclerosis Society; and his research is funded by Biogen, Deutsche Forschungsgemeinschaft, the Else Kröner Fresenius Foundation, the European Union, the Fresenius Foundation, the German Ministry for Education and Research (BMBF), GlaxoSmithKline GmbH, the Hertie Foundation, the Interdisciplinary Center for Clinical Studies (IZKF) Muenster and RE Children's Project, the NRW Ministry of Education and Research, Roche Pharma AG, and Sanofi-Genzyme.

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