Safety experience with extended exposure to ofatumumab in patients with relapsing forms of multiple sclerosis

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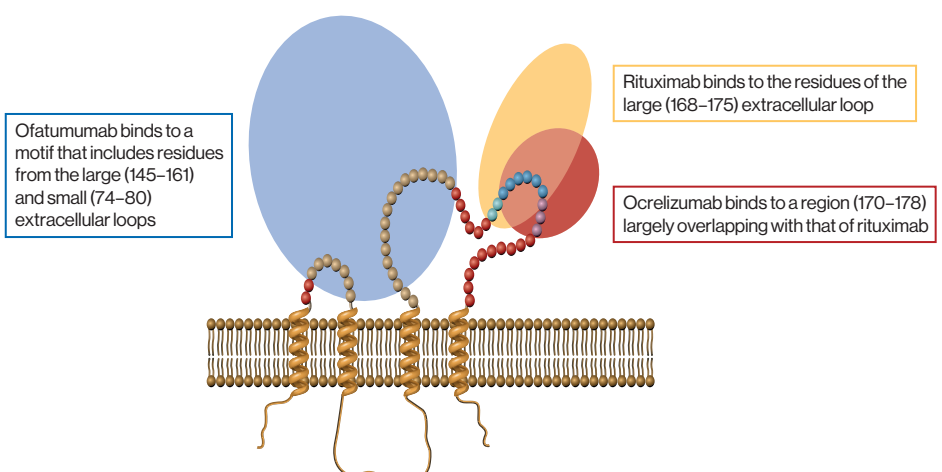
Ofatumumab was well tolerated, with no new safety risks identified.

What is ofatumumab?

- Ofatumumab, the **first fully human anti-CD20 monoclonal antibody**, is widely approved for the treatment of forms of relapsing MS (RMS). It induces B-cell depletion primarily through a mechanism called complement-dependent cytotoxicity.
- Owing to its high potency, distinct mode of action and subcutaneous delivery, ofatumumab has a good safety profile and is well tolerated.
- It can be self-administered after the initial dose has been given under medical supervision.



Who took part in this study?

- This study was called the ALITHIOS trial. It included people with RMS who had either relapsing–remitting MS or secondary progressive MS with disease activity. Participants had taken part in one of four previous trials could enter the ALITHIOS trial. The four previous trials were called ASCLEPIOS I, ASCLEPIOS II, APLIOS and APOLITOS.
- Participants were categorized as 'continuously treated' if they had received ofatumumab before the start of ALITHIOS, and as 'newly switched' group if they had not. The overall group of participants in ALITHIOS was called 'overall safety population'.

		Overall safety population (N = 1969)	
		Continuously treated ofatumumab (n = 1292)	Newly switched ofatumumab (n = 677)
ASCLEPIOS I	Ofatumumab, 465	355 entered ALITHIOS 110 completed/discontinued core study	
	Teriflunomide, 462		338 entered ALITHIOS
ASCLEPIOS II	Ofatumumab, 481	335 entered ALITHIOS 146 completed/discontinued core study	
	Teriflunomide, 474		339 entered ALITHIOS
APLIOS	Ofatumumab, 284	279 entered ALITHIOS 5 completed/discontinued core study	
APOLITOS	Ofatumumab, 62	57 entered ALITHIOS 5 completed/discontinued core study	
		ALITHIOS (N = 1703)	

- The overall safety population included 1969 participants, of whom 1292 were in the continuously treated ofatumumab group and 677 in the newly switched ofatumumab group.
- The median exposure to ofatumumab for the whole group was 21 months, with a range of 0–52 months. The median exposure in the continuously treated ofatumumab group was 35.5 months.

Did the study identify any risks associated with extended exposure to ofatumumab that were not known before?

In the overall safety population, this study did not identify any new risks associated with long-term treatment with ofatumumab that were not known before.

	EXPOSURE-ADJUSTED INCIDENCE per 100 patient-years (95% confidence interval)
At least one adverse event	**148.7 (141.7–156.1)**
At least one serious adverse event	**4.8 (4.1–5.5)**
Infection	**44.1 (41.5-46.8)**
Serious infection	**1.4 (1.1–1.8)**
Malignancy	**0.3 (0.1–0.5)**

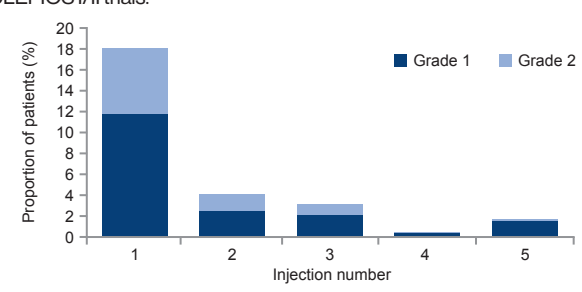
Exposure-adjusted incidence rates per 100 patient-years are defined as the number of patients with a particular event during 100 years of exposure to a treatment.

The most frequent infections in the overall safety population were:

- nasopharyngitis (16.8%)
- upper respiratory tract infections (10.3%)
- urinary tract infections (9.8%)
- COVID-19 (5.8%).

Did people who started taking ofatumumab have an increased risk of reactions to the injections?

- In the overall study population, 11.5% had a local injection-site reaction, and 24.8% had a systemic injection-related reaction (IRR).
- In the newly switched group, as shown below, most systemic IRRs were after the first dose; all systemic IRRs were mild or moderate, and they rarely led to withdrawal of ofatumumab.
- No life-threatening or anaphylactic injection reactions occurred.
- Rates of local injection-site and systemic IRRs were consistent with those previously reported in the phase 3 ASCLEPIOS I/II trials.

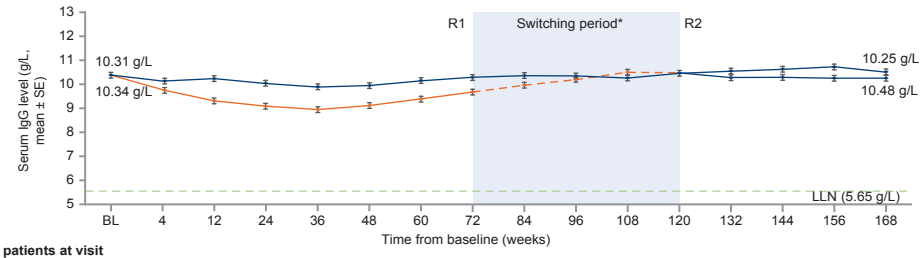


Injection-related systemic reactions by injection number in the newly switched group (first five injections).

Did the levels of IgG and IgM drop in a way that could potentially increase the risk of serious infection?

- Treatment with anti-CD20 antibodies has been shown to decrease the levels of immunoglobulin G (IgG) and immunoglobulin M (IgM), thus weakening the immune system and increasing the risk of serious infections.
- In this study, mean IgG levels remained stable after up to 3.5 years of treatment, while mean IgM levels decreased but remained above lower limit of normal (LLN).
- Overall, the incidence of serious infections was low, and there was no association between decreased immunoglobulin levels and the risk of serious infections.

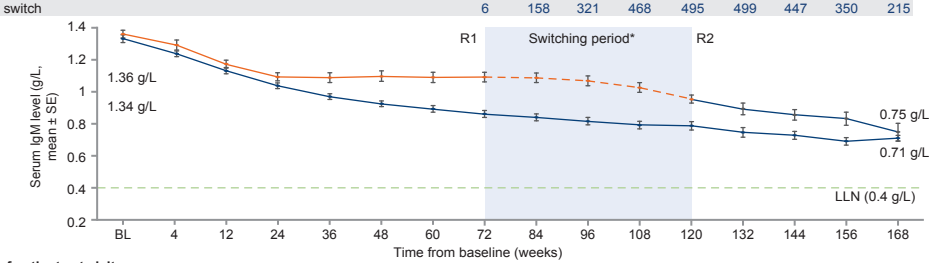
(a)



No. of patients at visit

	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168
Continuously treated ofatumumab	1269	1233	1248	1219	1180	1132	1083	902	961	758	712	602	514	469	345	241
Teriflunomide/ ofatumumab	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/ 6	477/ 158	313/ 321	167/ 468	72/ 495	499	447	350	215

(b)



No. of patients at visit

	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168
Continuously treated ofatumumab	1271	1235	1250	1221	1182	1134	1088	906	965	768	715	603	515	477	350	248
Teriflunomide/ ofatumumab	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/ 6	477/ 158	313/ 321	167/ 468	72/ 495	506	451	359	220

Serum immunoglobulin levels from baseline up to week 168 in the continuous and newly switched groups (safety analysis set). (a) IgG levels; (b) IgM levels.

Conclusion

The cumulative safety data suggest that extended treatment with ofatumumab is well tolerated in patients with RMS. Combined with its established effectiveness, these findings support a favourable benefit–risk profile for ofatumumab in all RMS patients.

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