Serum Immunoglobulin Levels and Infections in Relapsing Multiple Sclerosis

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Introduction

- Patients with multiple sclerosis (MS) are at an increased risk of infection compared with the general population[1]
- Immunoglobulins (Igs) play a major role in immunoprotection. In MS patients receiving disease-modifying, particularly B-cell depleting therapies[2-5], serum IgM and IgG levels below the lower limit of normal (LLN) have been associated with an increased risk of infection. Immunoglobulins have also been considered a biomarker for assessment of infection risk in MS
- Ofatumumab, a Food & Drug Administration-approved fully human anti-CD20 monoclonal antibody[6], with a monthly 20 mg subcutaneous (s.c.) dosing regimen,demonstrated superior efficacy versus teriflunomide 14 mg oral once daily, and a favourable safety profile in relapsing MS (RMS) patients in the Phase 3 ASCLEPIOS I/II trials[7]

Objective

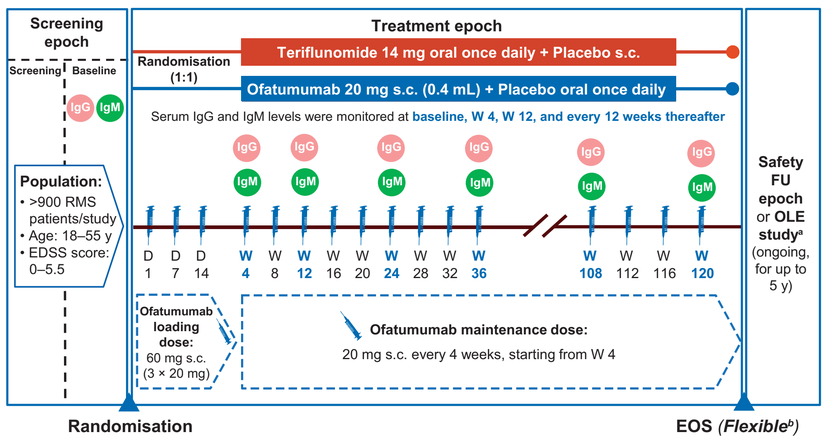
- To evaluate the frequency of abnormally low immunoglobulin assessments in the clincial study and the association between serum IgM and IgG levels, and risk of infections in the Phase 3 ASCLEPIOS I/II trials comparing ofatumumab versus teriflunomide in RMS patients

Methods

Study design

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

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



[a]OLE study (for up to 5 year) via 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 extension can have at least 9 months FU after the last dose of study drug

[b]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 randomised.

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

Study assessments

- Serum samples for IgM and IgG assessments (measured by immunoturbidometry) were collected at specified timepoints (baseline, Week (W) 4, W12, and every 12 weeks thereafter)(**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 analysed

- Number of patients who were screen failures due to immunoglobulin levels below the LLN
- Change in serum IgM and IgG levels from baseline
- Proportion of patients with IgM/IgG levels below the LLN (IgM, 0.4; IgG, 7.0 [g/L]) at any point during post-baseline visits
- Association of infections occurring in conjunction with a decrease in either IgM or IgG levels <LLN within 1 month prior and 1 month after detection of any series of decrease in IgM or IgG levels was observed and compared with reported infections in patients who maintained normal immunoglobulin levels (≥LLN)
- Analyses were performed on the safety set (all patients who received at least 1 dose of study medication)
- Treatment-emergent adverse events were summarised descriptively by treatment group

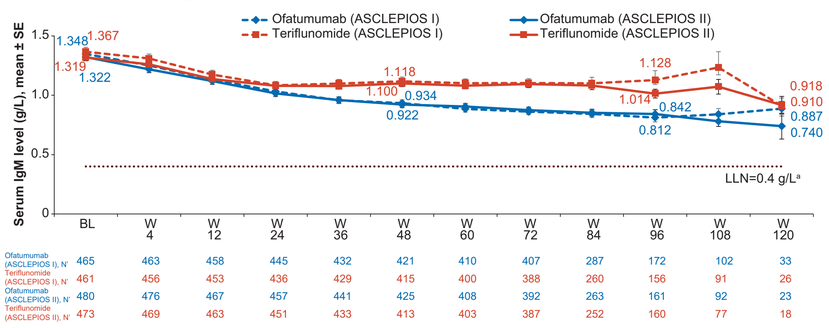
Results

- As per the protocol, the vast majority of patients (>99% in both groups) start with IgM or IgG ≥LLN at baseline
- Overall, 327 (ASCLEPIOS I) and 306 (ASCLEPIOS II) patients discontinued from study prior to randomisation and did not satisfy the inclusion/exclusion criteria
- Of these, the following patients were screen failures due to IgM/IgG <LLN
  - IgM <LLN: ASCLEPIOS I (n=19); ASCLEPIOS II (n=17)
  - IgG <LLN: ASCLEPIOS I/II (n=73, each)

Change in serum IgM levels from baseline

- A reduction in mean serum IgM levels from baseline was observed in both treatment groups in both studies
- A greater reduction of mean serum IgM was observed with ofatumumab treatment (ofatumumab: a decrease of 38.8% [–0.537 g/L] vs teriflunomide: a decrease of 20.0% [–0.282 g/L] among 96 week completers)
- Overall, mean serum IgM levels remained well above the LLN over time (patients aged between 16–19 years: 0.23 g/L; patients aged >19 years: 0.40 g/L; **Figure 2**)

Figure 2. Serum IgM levels from baseline over time

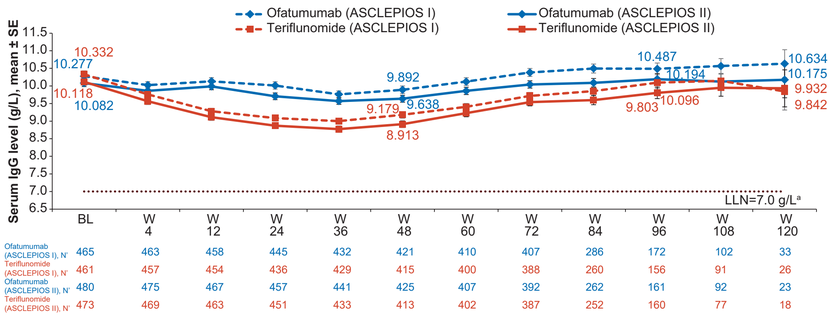


[a]For parameters with multiple reference ranges, reference range for females (since majority of the population is adult female) above 19 years of age is used to display the normal limit range. BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; SE, standard error; W, week

Change in serum IgG levels from baseline

- No reduction in the mean serum IgG was observed in 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 ofatumumab-treated patients
- A greater reduction of mean serum IgG was observed with teriflunomide treatment (ofatumumab: an increase of 2.2% [+0.249 g/L] vs teriflunomide: a decrease of 4.1% [–0.421 g/L] among 96 week completers)
- Overall, mean serum IgG levels remained well above the LLN over time (patients aged between 16–19 years: 5.49 g/L; patients aged >19 years: 7.00 g/L) (**Figure 3**)

Figure 3. Serum IgG levels from baseline over time

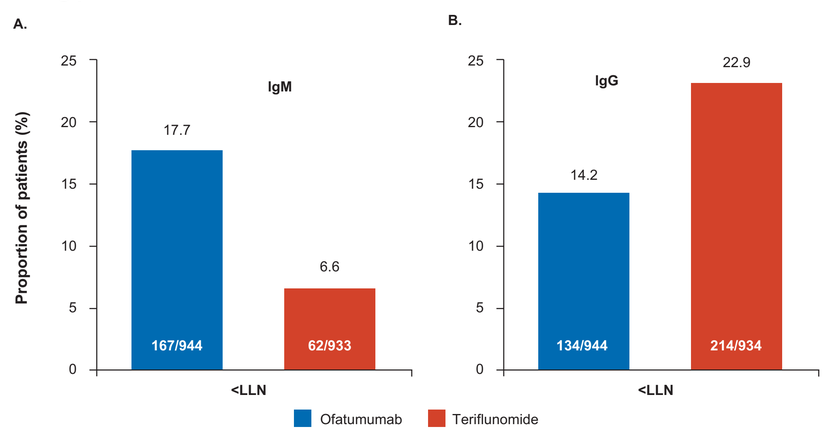


[a]For parameters with multiple reference ranges, reference range for females (since majority of the population is adult female) above 19 years of age is used to display the normal limit range. BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; SE, standard error; W, week

The proportion of patients reaching IgM/IgG levels below LLN at any time during post-baseline visits

- The proportion of patients with IgM levels below the LLN at anytime during post-baseline visits was higher among patients with ofatumumab (17.7%; 167/944) versus teriflunomide (6.6%; 62/933) **(Figure 4A)**
- The proportion of patients with IgG levels below the LLN at anytime during post-baseline visits was lower among patients with ofatumumab (14.2%; 134/944) versus teriflunomide (22.9%; 214/934) **(Figure 4B)**

Figure 4. The proportion of patients with IgM/IgG levels below LLN at any time during post-baseline visits



Ig, immunoglobulin; LLN, lower limit of normal

Incidence of infection that occurred within 1 month prior and 1 month after the drop in IgM level below the LLN

- The proportion of patients who experienced at least 1 infection between 1 month prior and 1 month after the drop in IgM levels below the LLN were comparable between ofatumumab and teriflunomide treatment groups (31.1% [52/167] vs 29.0% [18/62]) (**Table 1**)
  - A similar trend was observed in patients with IgM ≥LLN with ofatumumab (51.5%; 400/777) and teriflunomide (52.7%; 459/871)
- Among patients with IgM levels below the LLN, 2 patients (1.2%; 2/167) from the ofatumumab group experienced serious infections (upper respiratory tract and urinary tract infections); none were reported with teriflunomide
- Among patients with IgM levels ≥LLN, the proportion of patients who experienced serious infections was comparable between the treatment groups (ofatumumab, 2.3% [18/777] vs teriflunomide, 2.0% [17/871])
- The majority of infections observed with ofatumumab treatement were non-serious and mild-to-moderate in severity
- No opportunistic infections were reported in either treatment group

Table 1. Infections observed in patients within 1 month prior and 1 month after the drop in IgM levels below the LLN

	IgM <LLN		IgM ≥LLN	
	Ofatumumab (N=167[a]) n (%)	Teriflunomide (N=62[a]) n (%)	Ofatumumab (N=777[b]) n (%)	Teriflunomide (N=871[b]) n (%)
Patients with at least one infection	**52 (31.1)**	**18 (29.0)**	**400 (51.5)**	**459 (52.7)**
Patients with at least one serious infection	2 (1.2)	0	18 (2.3)	17 (2.0)
Upper respiratory tract infection (PT)	1 (0.6)	0	0	0
Urinary tract infection (PT)	1 (0.6)	0	2 (0.3)	2 (0.2)
Escherichia urinary tract infection (PT)	0	0	1 (0.1)	0
Kidney infection (PT)	0	0	1 (0.1)	0
Pneumonia (PT)	0	0	1 (0.1)	1 (0.1)

[a]Number of patients with IgM <LLN at least once at any time during the post-baseline visits; [b]Number of patients with no occurrence of IgM <LLN at least once at any time during the post baseline visit. Ig, immunoglobulin; LLN, lower limit of normal; n, number of evaluable patients; PT, preferred-term

Incidence of infections that occurred within 1 month prior and 1 month after the drop in IgG below the LLN

- The proportion of patients who experienced at least 1 infection within 1 month prior and 1 month after the drop in IgG levels below the LLN were comparable between ofatumumab and teriflunomide treatment groups (27.6% [37/134] vs 29.4% [63/214]) (**Table 2**)
  - A similar trend was observed in patients with IgG levels ≥LLN treated with ofatumumab (50.6%; 410/810) and teriflunomide (52.4%; 377/720)
- Among patients with IgG levels below the LLN, 3 patients (2.2%; 3/37) treated with ofatumumab experienced serious infections (upper respiratory tract infection, Escherichia urinary tract infection, kidney infection and pneumonia) and none were reported with teriflunomide treatment
- Among patients with IgG levels ≥LLN, a higher proportion of patients with ofatumumab (2.6%; 21/810) experienced serious infections compared with teriflunomide (1.9%; 14/720)
- The majority of infections observed with ofatumumab treatement were non-serious and mild-to-moderate in severity
- No opportunistic infections were reported in either treatment group

Table 2. Infections observed in patients within 1 month prior and 1 month after the drop in IgG below LLN

	IgG <LLN		IgG ≥LLN	
	Ofatumumab (N=134[a]) n (%)	Teriflunomide (N=214[a]) n (%)	Ofatumumab (N=810[b]) n (%)	Teriflunomide (N=720[b]) n (%)
Patients with at least one infection	**37 (27.6)**	**63 (29.4)**	**410 (50.6)**	**377 (52.4)**
Patients with at least one serious infection	3 (2.2)	0	21 (2.6)	14 (1.9)
Upper respiratory tract infection (PT)	1 (0.7)	0	0	0
Urinary tract infection (PT)	0	0	3 (0.4)	1 (0.1)
Escherichia urinary tract infection (PT)	1 (0.7)	0	0	0
Kidney infection (PT)	1 (0.7)	0	0	0
Pneumonia (PT)	1 (0.7)	0	0	1 (0.1)

[a]Number of patients with IgG <LLN at least once at any time during the post-baseline visits; [b]Number of patients with no occurrence of IgG <LLN at least once at any time during the post baseline visit. Ig, immunoglobulin; LLN, lower limit of normal; n, number of evaluable patients; PT, preferred-term

Conclusions

- Average serum IgM/IgG levels remained well within the reference ranges over time in both treatment groups
  - A reduction in the mean serum IgM levels from baseline was observed over time in few patients, but for the majority of the patients, levels remained above the LLN
  - There was no decrease in mean IgG levels from baseline over time
- There was no observed association between a decrease in immunoglobulin levels and the incidence of infections in both ofatumumab- and teriflunomide-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 infections reported were non-serious in nature and were mild to moderate in severity; most cases were resolved while patients were continuing treatment
- Assessing immunoglobulin levels prior to and during initiation of anti-CD20 therapy is important, but additional long-term studies are needed to elucidate the frequency and implications of low immunoglobulin levels at baseline and during treatment

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