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

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Background

Ofatumumab, a fully human anti-CD20 monoclonal antibody, demonstrated superior efficacy vs teriflunomide with a favorable safety profile in relapsing MS (RMS) patients in the Phase 3 ASCLEPIOS I/II trials. Reductions in serum immunoglobulin (Ig) M and IgG levels are associated with anti-CD20 therapies.

Objective

To assess the effect of ofatumumab on serum Ig levels and evaluate potential association between a decrease in IgM/IgG levels and risk of infections.

Methods

Patients were randomized to receive subcutaneous ofatumumab 20 mg (initial doses: Days 1, 7, and 14; subsequent doses: every 4 weeks from Week (W) 4 onwards) or oral teriflunomide 14 mg once-daily for up to 30 months (m, mean follow-up duration: 18m). Serum IgM/IgG levels were monitored at baseline (BL), W4, W12, and every 12 weeks thereafter (ofatumumab, n=946; teriflunomide, n=936). Proportion of patients with IgM/IgG levels below the lower limit of normal (<LLN [g/L]: IgM, 0.4; IgG, 7.0), and association of IgM/IgG levels with incidence of infections that occurred up to 1m prior and 1m after any decrease in IgM/IgG levels (<LLN vs ≥LLN) were analyzed. Infections in conjunction with IgM/IgG <LLN and lymphopenia and/or neutropenia on the same visit were also analyzed.

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Results

Mean IgM/IgG levels were well within reference ranges over time. Over all post-BL visits, a higher proportion of patients on ofatumumab had IgM<LLN (17.7% vs 6.6%), whilst a lower proportion had IgG<LLN (14.2% vs 22.9%) vs patients on teriflunomide. At W96, a similar trend was observed (IgM<LLN: 11.1% vs 1.9%; IgG<LLN: 2.7% vs 6.0%). Proportion of patients on ofatumumab who experienced ≥1 infection within 1m prior and until 1m after IgM<LLN was 31.1% (52/167; 2 serious) vs 51.5% (400/777) with IgM≥LLN (18 serious). Similarly, 27.6% (37/134) reported infections during a drop in IgG<LLN (3 serious) vs 50.6% (410/810) with IgG≥LLN (21 serious). The most common infection was nasopharyngitis. Overall, 1/11 patients with concurrent IgM<LLN and lymphopenia and/or neutropenia, and 7/20 patients with concurrent IgG<LLN and lymphopenia and/or neutropenia reported infections; none were serious.

Conclusion

Reduction in serum IgM levels was observed over time, but for the majority of patients, Ig levels remained above the lower limit of normal. No decrease in IgG levels was reported within the observation period (mean follow-up: 18m). There was no apparent association between decreased Ig levels and infections in conjunction with lymphopenia and/or neutropenia in ofatumumab-treated RMS patients.

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