Dose-dependent tolerability of intravenous and subcutaneous ofatumumab in clinical studies

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Background

Ofatumumab, a fully human anti-CD20 monoclonal antibody with monthly 20 mg subcutaneous (s.c.) dosing regimen, demonstrated superior efficacy vs teriflunomide and a favorable safety profile in relapsing MS (RMS) patients in the Phase 3 ASCLEPIOS I/II trials. Prior studies evaluated the effect of >20 mg ofatumumab doses, s.c. and intravenous (i.v.), in both MS and rheumatoid arthritis (RA) patients. Injection/infusion-related reactions (IRRs) were the most frequently reported adverse events in these studies.

Objective

To assess the dose-dependent tolerability of different ofatumumab doses (s.c. and i.v.) in both patients with MS and with RA.

Methods

For MS, data were pooled from ASCLEPIOS I/II, APLIOS (s.c. ofatumumab 20 mg, N=1873 including long-term data), Phase 2 dose-finding (i.v. ofatumumab 100 mg, N=12; 300 mg, N=15; 700 mg, N=11) and MIRROR studies (s.c. ofatumumab every 12 weeks [q12w]: 3 mg, N=34; 30 mg, N=32; 60 mg, N=34; 60 mg every 4 weeks [q4w], N=64). For RA, data were pooled from Phase 1/2/3 studies administered with atleast 1 dose of i.v. ofatumumab (300 mg, N=70; 700 mg, N=282; 1000 mg, N=64) up to Week 24. IRRs were reported within 24 hours of dose administration. Tolerability was measured as IRR-related drug interruption, discontinuation, severity and seriousness.

Results

In MS patients, the incidence of IRRs was lowest with s.c. 20 mg (23.2%) vs all other effective doses. The majority (99.8%) of IRRs with s.c. 20 mg were Grade 1/2 in severity. Grade 3 IRRs were lower with s.c. 20 mg (0.2%) vs all other doses (1.6–18.2%). No drug interruptions were observed across s.c. doses while the drug was interrupted (paused and restarted) in 41.7–72.7% patients with i.v. doses. A lower proportion of patients withdrew treatment with s.c. 20 mg (0.1%) vs other doses (1.6–6.7%). Serious IRRs were low with s.c. 20 mg (0.1%) vs 60 mg doses (q12w, 2.9%; q4w, 3.1%); none were reported with all other doses. Two serious IRRs (of

1873 patients) with s.c. 20 mg occurred at first injection, resolved without treatment withdrawal and with no recurrences. Cytokine release syndrome was reported in 3 patients (s.c. 60 mg q12w, n=1 [hospitalized for observation]; i.v. 300 mg, n=2 [non-serious]). In RA patients, the incidence of IRRs was higher with i.v. 1000 mg (at first infusion: 71.9%), vs 300 mg (55.7%) and 700 mg (36.9%). The majority of IRRs were Grade 1/2 in severity (95.2%), non-serious (96.9%) and subsided with treatment; 8.4% discontinued treatment due to IRRs.

Conclusions

Ofatumumab 20 mg s.c. was well tolerated compared to higher s.c. and i.v. doses. IRRs were predominant with first injection and similar to matching-placebo with subsequent injections. Most IRRs were non-serious and mild-to-moderate in severity. The IRRs were manageable with low withdrawal rate and recovered with symptomatic treatment, even in absence of premedication. For MS, low dose s.c. injections have a better tolerability profile with higher compliance.

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Presentation preference

✓ Poster presentation

✓ Oral presentation

Disclosure of conflict of interest

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