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

Amit Bar-Or\textsuperscript{1}, Agnes Annette Schubert-Tennigkeit\textsuperscript{2}, Nicole Mairon\textsuperscript{2}, Cecile Kerloeguen\textsuperscript{2}, Mohammad Gufran\textsuperscript{3}, Shima Shaikh\textsuperscript{3}, Ayan Das Gupta\textsuperscript{3}, Eswara Gunisetti\textsuperscript{3}, Gisbert Weckbecker\textsuperscript{2}, Wendy Su\textsuperscript{4}, Krishnan Ramanathan\textsuperscript{2}, Ratnakar Pingili\textsuperscript{4}

\textsuperscript{1}Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; \textsuperscript{2}Novartis Pharma AG, Basel, Switzerland; \textsuperscript{3}Novartis Healthcare Pvt. Ltd., Hyderabad, India; \textsuperscript{4}Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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 at least 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.

**Character count with spaces (excluding headers):** 2410/2500

**Funding statement:** This study was funded by Novartis Pharma AG, Basel, Switzerland.

**Submission requirements**

**Presentation preference**

- **✔** Poster presentation  
- **✔** Oral presentation

**Disclosure of conflict of interest**

Amit Bar-Or has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Janssen/Actelion; Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Roche/Genentech, Medimmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme. Agnes Annette Schubert-Tennigkeit, Nicole Mairon, Cecile Kerloeguen, Mohammad Gufran, Shima Shaikh, Ayan Das Gupta, Eswara Gunisetti, Gisbert Weckbecker, Wendy Su, Krishnan Ramanathan and Ratnakar Pingili are employees of Novartis.

**Abstract Topic**

- Biomarkers and Bioinformatics  
- Biosensors  
- Biostatistical Methods  
- Clinical Outcome Measures  
- Clinical Trials  
- Comorbidities  
- Diagnostic Criteria and Differential Diagnosis  
- Disease Modifying Therapies – Mechanism of Action
• Disease Modifying Therapies – Risk Management
  • Epidemiology
  • Experimental Models
  • Gender Differences, Hormones and Sex Chromosomes
  • Genetics and Epigenetics
  • Imaging
  • Internet and Social Media
  • Machine Learning/Network Science
  • Microbiome
  • Metabolomics
  • Neuromyelitis Optica and Anti-MOG Disease
  • Neuro-Ophthalmology
  • Neuroprotection, Regeneration and/or Remyelination
  • Neuropsychology and Cognition
  • Observational Studies
  • Pathogenesis – Immunology
  • Pathogenesis – Neurodegeneration
  • Pathogenesis – Role of Glia
  • Pathogenesis – the Blood-Brain Barrier
  • Pediatric MS
  • Prognostic Factors
  • Patient-Reported Outcomes and Quality of Life
  • Rehabilitation and Comprehensive Care
  • Reproductive Aspects and Pregnancy
  • Symptom Management