KYRIOS clinical trial: Tracking the immune response to SARS-CoV-2 mRNA vaccines in an open-label multicenter study in participants with relapsing multiple sclerosis treated with ofatumumab s.c.

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Disclosures

Tjalf Ziemssen has received research support, consulting fee, and honoraria for lectures from Alexion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, Teva.

Tobias Bopp has received consulting fee and honoraria for lectures from Biogen, Celgene, Merck, Novartis, Pathios Therapeutics, Roche, Sanofi Genzyme, Teva.

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Background

- Development of SARS-CoV-2 vaccines was a key milestone in fighting the COVID-19 pandemic, but little is known about the efficacy of these vaccines in patients with Multiple Sclerosis (MS) treated with anti-CD20 therapies.

- Ofatumumab is the first fully-human anti-CD20 antibody authorized by the EMA for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease. Ofatumumab is applied once monthly s.c. (20 mg) and selectively depletes B-cells, which represent one pillar of the adaptive immune response.

- However, newly developed SARS-CoV-2 mRNA vaccines have been shown to not only induce selective B- but also T-cell responses[1,2].

- **Thus, it becomes essential to investigate both, humoral and cellular immune responses in patients treated with ofatumumab in order to provide guidance on vaccination for patients with MS and treating physicians**.

1. Sahin et al. (2021) Nature. 595,572–577. **2.** Jackson et al. (2020) N Engl J Med. 383:1920-1931.

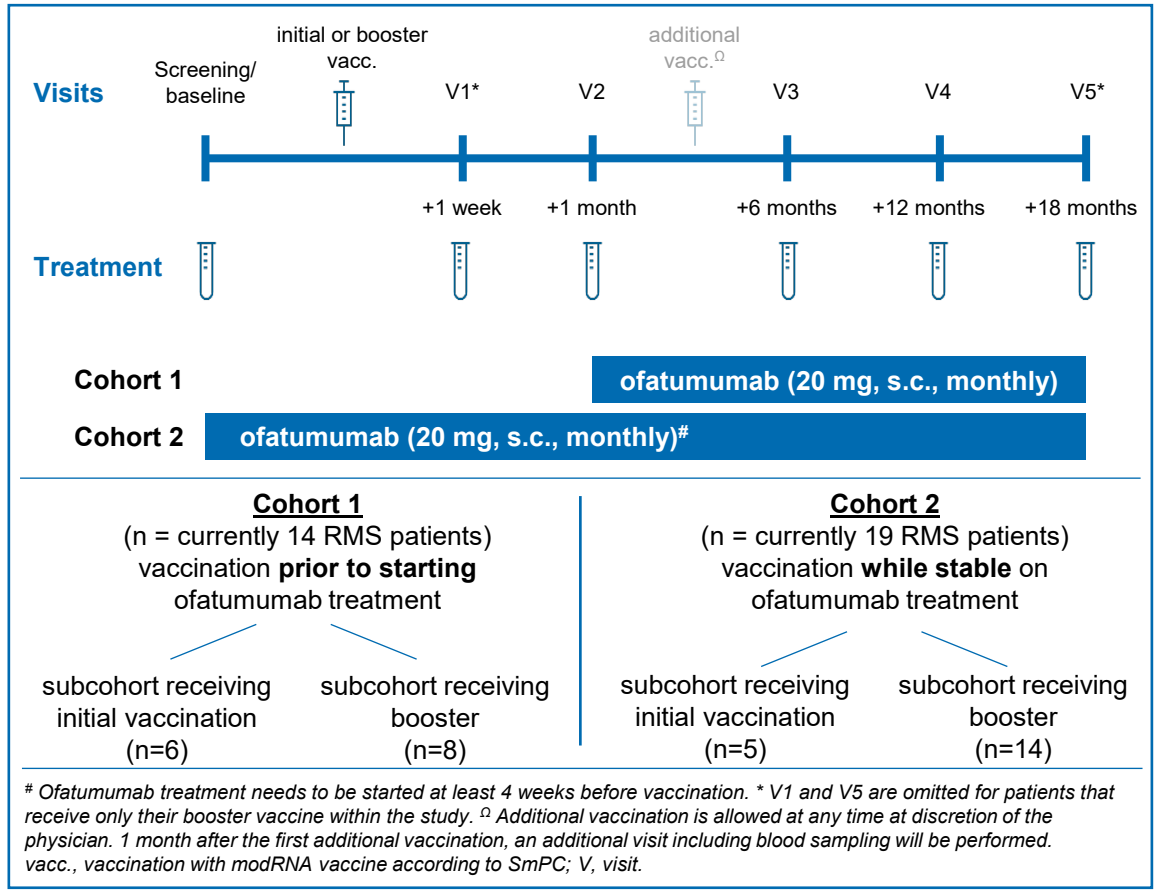
Objective

The aim of this study is to understand the impact of ofatumumab treatment on mounting cellular and humoral immune responses after initial and booster SARS-CoV-2 mRNA vaccination.

Methods

- KYRIOS is a two-cohort, open-label, prospective study currently including 33 RMS patients at 8 sites in Germany (**Figure 1**).
  - This study compares the immune response in patients receiving SARS-CoV-2 mRNA vaccination prior to starting ofatumumab treatment (**cohort 1, control cohort**) and patients vaccinated during stable ofatumumab treatment for at least 4 weeks (**cohort 2**).
  - Immune responses after initial and booster vaccination were analyzed separately.
- Ofatumumab treatment is administered as part of the study and vaccinations as part of clinical routine according to summary of product characteristics (SmPC).
- **Neutralizing antibodies** were analyzed utilizing the cPassTMSARS-CoV-2 Neutralization Antibody Detection Kit from GenScriptUSA Inc(L00847).
- **SARS-CoV-2 specific T-cells** were detected with the CoV-iSpot Interferon-γ + Interleukin-2 (ELSP 7010 strip format) from GenID®GmbH. Each ELISpot assay was performed with $2x10^6$ PBMCs (peripheral blood mononuclear cells).

Figure 1: Study design



*# Ofatumumab treatment needs to be started at least 4 weeks before vaccination. * V1 and V5 are omitted for patients that receive only their booster vaccine within the study. Ω Additional vaccination is allowed at any time at discretion of the physician. 1 month after the first additional vaccination, an additional visit including blood sampling will be performed. vacc., vaccination with modRNA vaccine according to SmPC; V, visit.*

Demographics and baseline information

- Patient characteristics at the time of screening are shown in **Table 1**.
  - There are currently 33 patients enrolled in the study with an average age of 41.6 years and a disease history of 6.7 years.
  - 50% in cohort 1 and 26% in cohort 2 were treatment naive.
- Most patients received BioNTech/Pfizer SARS-CoV-2 mRNA vaccines with an average of 4.8 weeks between 1st and 2nd dose.
- Booster vaccines were administered on average 6.1 months after 2nd dose and mostly (90%) with the same vaccine as in the initial vaccination cycle.
- B-cell depletion was verified in subjects of cohort 2 before vaccination.

Table 1: Patient characteristics

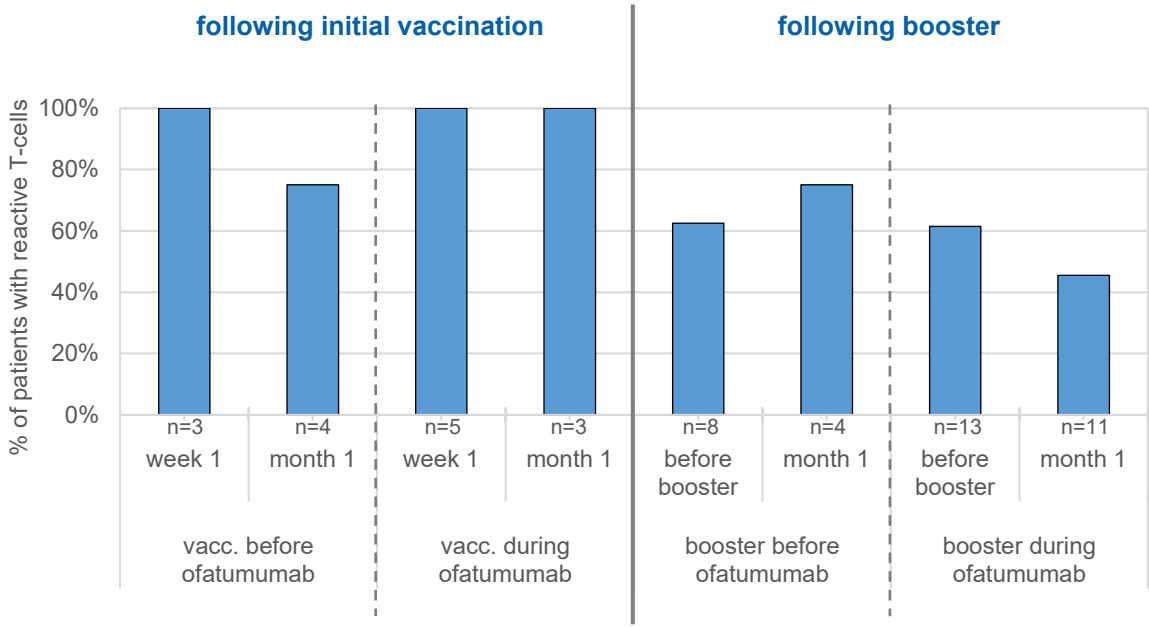
Variable*	Cohort 1 – vaccination prior to treatment	Cohort 2 – vaccination during stable treatment
N	14	19
Age, years	40.84 [23; 79]	42.08 [21; 61]
Sex, female, n (%)	10 (41.7)	11 (61.1)
Time since diagnosis, years	7.5 [0; 23]	6.1 [0; 19]
Prior treatments before ofatumumab Naive, N (%) One, N (%) Two, N (%) More than two, N (%)	 7 (50) 2 (14.3) 0 (0) 5 (35.7)	 5 (26.3) 4 (21.1) 5 (26.3) 5 (26.3)
Vaccination, n (%) 1st (BioNTech | Moderna) 2nd (BioNTech | Moderna) Booster (BioNTech | Moderna)	 13 (92.9) | 1 (7.1) 13 (92.9) | 1 (7.1) 7 (87.5) | 1 (12.5)	 18 (94.7) | 1 (5.3) 18 (94.7) | 1 (5.3) 11 (84.6) | 2 (15.4)
Vaccination time interval (days) 1st to 2nd vaccination 2nd vaccination to Booster	 30.8 [21; 42] 182 [160; 216]	 35.7 [21; 56] 187 [129;295]
CD19+/CD20+ cells at baseline (cells/µl)	215.7 [7; 535]	0.1 [0;1]

* if not indicated otherwise, data are presented as mean [min; max]; #depending on subcohort vaccine refers to either initial vaccination or booster vaccination

SARS-CoV-2 specific T-cell response

- All patients (5/5) receiving initial vaccination during stable ofatumumab treatment developed SARS-CoV-2 reactive T-cells (**Figure 2**).
- Extend of T-cell response in these patients was comparable to control cohort and peaked at 1 week after vaccination (data on file).
- T-cell response in boostered patients was comparable in both cohorts.
- Across both cohorts, most patients without T-cell response after booster (5/7) were older than 50 years.
- As this is an interim analysis, T-cell data after booster is still incomplete and needs to be interpreted with caution.

Figure 2: SARS-CoV-2 T-cell reactivity (IFN-γ and/or IL-2)

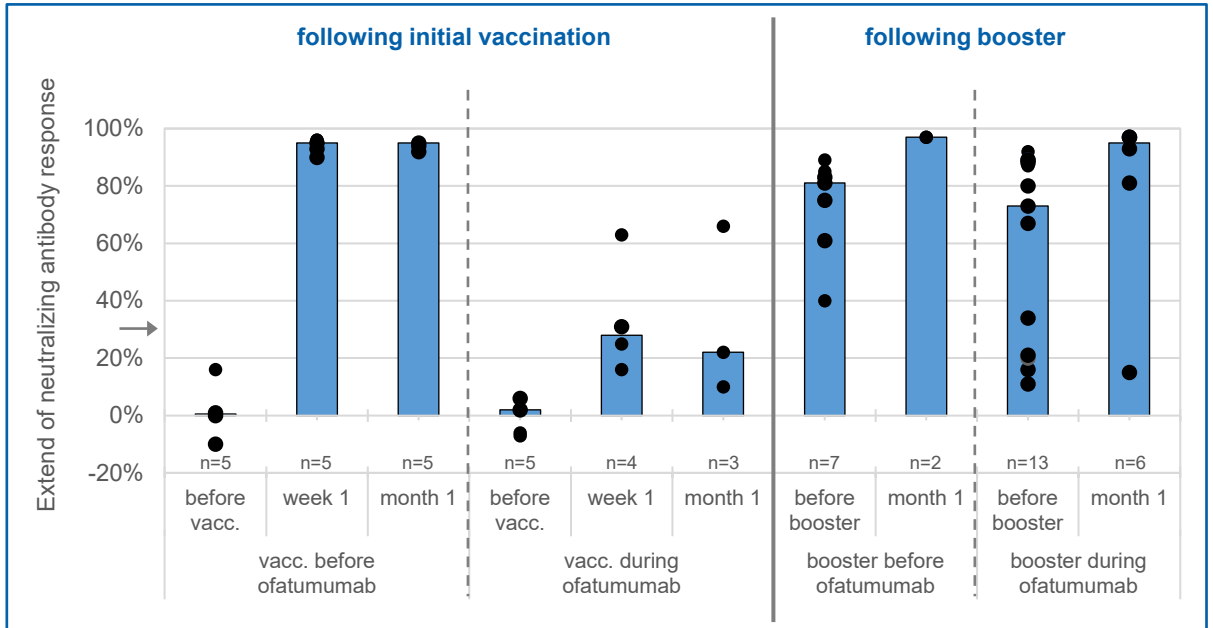


T-cell response measured by secretion of IFN-γ and/or IL-2 (ELIspot) after stimulation of isolated PBMCs with SARS-CoV-2 peptide mix. T cell response was defined as present if at least one of the parameters INF-γ or IL-2 were positive or equivocal. n = All patients that passed the respective time points were included in the analysis. vacc., vaccination

Development of SARS-CoV-2 neutralizing antibodies

- Neutralizing antibodies (NAb) represent only **a subset of all specific antibodies** and are considered a **more stringent** correlate of protective immunity. Total anti-SARS-CoV-2 IgGs were not measured here but might further contribute to immunity.
- All patients (4/4) receiving their initial vaccination during stable ofatumumab treatment had an increase in NAb (**Figures 3**).
- 50% of ofatumumab patients exceeded the assay-specific cut-off for seropositivity one week after vaccination.
- 5/6 patients boostered during stable ofatumumab treatment showed an increase in NAb to a similar extend as in control group.
- One patient who was seronegative before booster seroconverted during stable ofatumumab treatment.

Figure 3: Development of SARS-CoV-2 neutralizing antibodies



Extend of neutralizing antibody response indicats the proportion of inhibited in vitro binding of purified Receptor Binding Domain (RBD) of SARS-CoV-2 spike protein and ACE2 receptor by patient serum. Bars represent medians; all patients with available data were included in the analysis and individual values are represented by dots. Arrow indicates the the assay-specific cut-off for seropositivity of 30%. vacc., initial vaccination

Safety

- One MS relapse occurred during the study (patient in cohort 2, relapse occurred before 1st vaccination, patient recovered fully)
- Two patients developed COVID-19 infections during the study:
  - One patient in cohort 1 (initial vaccination prior to ofatumumab treatment): 6 days after 2nd vaccination, CTCAE moderate, no MS therapy at time of infection, full recovery (duration of infection: 9 days)
  - One patient in cohort 2 (initial vaccination during ofatumumab treatment): 27 days after 2nd vaccination, CTCAE moderate, no interruption of ofatumumab treatment, infection was ongoing at time of data cut-off but has by now fully recovered (duration of infection: 13 days)

Conclusions

- **All patients (5/5) vaccinated during continuous ofatumumab treatment developed an immune response as soon as one week after initial vaccination cycle.**
  - T-cell response was not affected by ofatumumab treatment and similar to control cohort
  - All patients showed an increase in neutralizing antibodies. Although the extent was lower versus control group, 50% exceeded the cut-off value for seropositivity.
  - These results are in line with previously reported low rate of COVID-19 infections in vaccinated patients treated with ofatumumab[3]
- **Immune response after booster vaccine was similar in patients boostered before and during ofatumumab treatment.**
  - 6/7 ofatumumab patients had increased neutralizing antibodies to a comparable extend as in control cohort
  - one patient who was seronegative before booster seroconverted during continuous ofatumumab treatment
  - T-cell response was heterogenous but comparable between cohorts. However, T-cell data is still incomplete and needs to be interpreted with caution.
- Despite limited sample size, population heterogeneity and pending longitudinal data, we can conclude that both cellular and humoral response need to be considered for interpretation of vaccine efficacy.

3. Cross et al. (2022) *Neurology and Therapy*