Poster presented at the 9th Joint ECTRIMS-ACTRIMS Meeting, 11–13 October 2023 Milan, Italy.

P316

Immune response to SARS-CoV-2 mRNA booster vaccinations in relapsing multiple sclerosis patients treated with ofatumumab s.c.– Final results from the open-label multicenter KYRIOS trial

Tjalf Ziemssen[1], Eugen Schlegel[2], Veronika E. Winkelmann[3], Lea Leist[3],Tobias Bopp[4]

[1]Department of Neurology, Center of Clinical Neuroscience, Carl Gustav Carus University Clinic, University Hospital of Dresden, Fetscherstr. 74, 01307, Dresden, Germany. [2]Zentrum für neurologische Studien, 57076 Siegen, Deutschland. [3]Novartis Pharma GmbH, Roonstr. 25, D-90429 Nuernberg, Germany. [4]Institute for Immunology, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany

SUMMARY

1. KYRIOS study examines how ofatumumab treatment impacts cellular and humoral immune responses to initial and booster SARS-CoV-2 mRNA vaccines in multiple sclerosis (MS) patients.
2. The study involves 34 MS patients in two cohorts. Patients received initial or booster SARS-CoV-2 mRNA vaccine before (cohort 1) or at least 4 weeks after (cohort 2) starting ofatumumab treatment. Immune responses were monitored for up to 18 months.
3. Ofatumumab didn't affect T-cell response post-initial and first booster vaccination. Neutralizing antibodies in ofatumumab treated patients increased after initial vaccination, albeit lower than in control cohort. Booster-induced neutralizing antibody response was similar in patients boosted before/during ofatumumab treatment, including seroconverted cases.
4. KYRIOS data demonstrate that ofatumumab treated patients can mount specific immune responses towards initial and booster SARS-CoV-2 mRNA vaccines. Data underscores need to account for both humoral and cellular immune responses when assessing vaccine efficacy and emphasizes booster importance in immunocompromised patients.

INTRODUCTION

- Initial and booster vaccination with the newly developed SARS-CoV-2 mRNA vaccines efficiently protect healthy individuals against COVID-19, 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.
- With regards to the newly developed SARS-CoV-2 mRNA vaccines it could however been shown that they not only induce selective B- but also T-cell responses[1,2].

OBJECTIVE

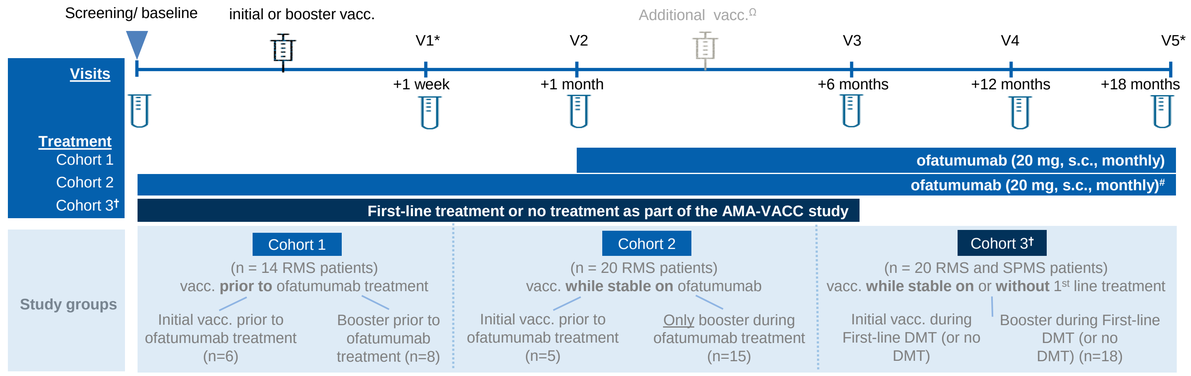
- The aim of this study is therefore to understand the **impact of ofatumumab treatment** on mounting **cellular and humoral immune responses** after initial and booster **SARS-CoV-2 mRNA vaccination**.

METHODS

STUDY DESIGN

- KYRIOS is a prospective, open-label, two-cohort study including 34 RMS patients at 8 sites in Germany **(Figure 1)**.
- Final results are demonstrated.
  - Patients receive initial or booster SARS-CoV-2 mRNA vaccination either before (**control cohort /cohort 1**) or at least 4 weeks after starting ofatumumab treatment (**cohort 2**). Additionally, 20 patients from AMA-VACC study[3] (**cohort 3**) who received SARS-CoV-2 mRNA booster vaccination during first-line treatment or no treatment were included in the final analysis.
  - 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). A second booster vaccination was administered if necessary.
- Neutralizing antibodies (NAb) were analyzed utilizing the cPassTMSARS-CoV-2 Neutralization Antibody Detection Kit from GenScriptUSA Inc(L00847). Total anti-spike antibody titers were measured using Elecsys Anti-SARS-CoV-2 S immuno-assay from Roche.
- 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 2x10^5 PBMCs (peripheral blood mononuclear cells).

Figure 1. Study design



(A) # 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 and second additional vaccination, an additional visit including blood sampling will be performed. † Patients part of the AMA-VACC study. vacc., vaccination with modRNA vaccine according to SmPC; V, visit.

RESULTS

DEMOGRAPHICS AND BASELINE INFORMATION

- Patient characteristics at the time of screening are shown in **Table 1**.
  - In total, 34 patients were enrolled in the study with a mean age of 41.6 years and a disease history of 6.5 years.
  - 50% of patients in cohort 1 and 40% in cohort 2 were treatment naive.
- > 90% of 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 5.7 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.

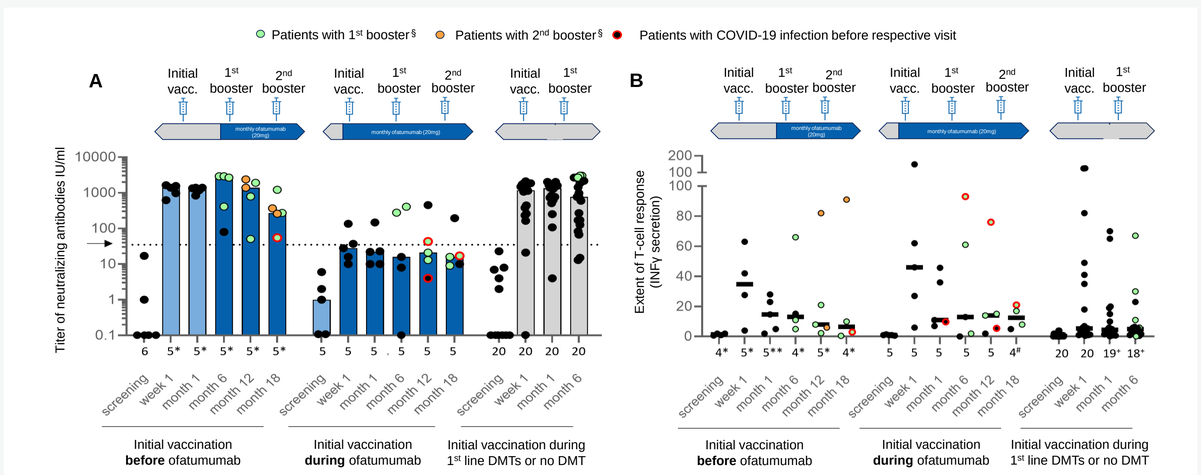
Table 1. Patient characteristics

Variable [min; max]	Cohort 1 – vaccination prior to treatment	Cohort 2 – vaccination during stable treatment	Cohort 3 – Booster vaccination during stable treatment or no treatment
N	14	20	20
Age, years	40.9 [23; 79]	42.2 [21; 61]	51 [22; 71]
Sex, female, n (%)	10 (71.4)	13 (65.0)	16 (80.0)
Time since first MS diagnosis, years	7.5 [0; 23]	5.8 [0; 19]	9.13 [3.2; 37.9]
MS diagnosis, n (%)	14 [100]	20 [100]	2 [10]
SPMS, active SPMS	-	-	12 [60]
RRMS, active RRMS	-	-	6 [30]
Prior treatments before ofatumumab			
Naive, n (%)	7 (50.0)	8 (40.0)	0 (0)
One, n (%)	2 (14.3)	5 (25.0)	20 (100)
Two, n (%)	0 (0.0)	6 (30.0)	-
More than two, n (%)	5 (35.7)	1 (5.0)	-
Vaccination, n (%)			
1st (BioNTech | Moderna)	13 (92.9) | 1 (7.1)	19 (95.0) | 1 (5.0)	19 (95.0) | 1 (5.0)
2nd (BioNTech | Moderna)	13 (92.9) | 1 (7.1)	19 (95.0) | 1 (5.0)	19 (95.0) | 1 (5.0)
Booster (BioNTech | Moderna | no booster documented)	7 (50.0) | 1 (7.1) | 0 (0.0)	13 (65.0) | 2 (10.0) | 0 (0.0)	11 (55.0) | 7 (35.0) | 2 (10.0)

SARS-COV-2 SPECIFIC T-CELL RESPONSE AND DEVELOPMENT OF NEUTRALIZING ANTIBODIES AFTER INITIAL VACCINATION CYCLE

- All patients (5/5) receiving their initial vaccination during stable ofatumumab treatment had an increase in NAb (**Figure 2A)** but to a lower extent than in the control cohorts.
- First trend shows that booster vaccination even when applied approx. 6 months after initial vaccination cycle distinctly increased the level of neutralizing antibodies in ofatumumab-treated patients (green dots).
- Titers at month 12 and month 18 are difficult to interpret due to very heterogenous populations (patients with none, one or two booster and/or COVID-19 infections).
- All patients (5/5) receiving initial vaccination during stable ofatumumab treatment developed SARS-CoV-2 reactive T-cells as soon as 1 week after full vaccination. Extent of T-cell response peaked at 1 week after full vaccination and was comparable between cohorts and similar to response in patients vaccinated during 1st line DMT or no DMT (**Fig. 2B**).

Figure 2: Immune response in patients with initial vaccination cycle before vs. during stable ofatumumab treatment

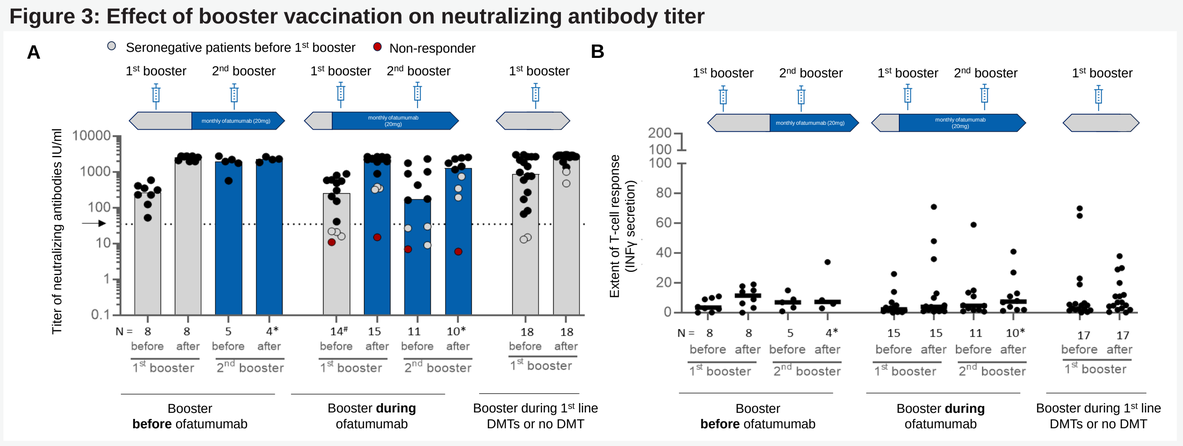


(A) Figure shows titer of neutralizing antibodies. Individual values are represented by dots and bars show median values, black arrows indicate assay-specific cut-off for seropositivity. *n=1 patient discontinued the study. **(B)** Extent of T-cell response represents the IFN-γ stimulation index. Each dot represents one patient, medians are indicated by horizontal lines. All available values were included in the analysis. Cohort 1: *For two patients at baseline and one patient at week 1, month 6 and month 18, respectively, T-cell response could not be assessed due to technical problems. One patient in cohort 1 discontinued the study and skipped all visits except month 1. **For one patient at month 1, visit could not be performed due to a COVID-19 infection. Cohort 2: # For one patients at month 18, T-cell response could not be assessed due to a technical problem. Cohort 3: +For one patient at month 1 and two patients at month 6, T-cell response could not be evaluated due to technical problems. §Booster vaccinations were allowed at any time during the study.

SARS-COV-2 SPECIFIC T-CELL RESPONSE AND DEVELOPMENT OF NEUTRALIZING ANTIBODIES AFTER BOOSTER VACCINATION

- Of those patients in this analysis have received their initial vaccination prior to study start during their previous DMT or no DMT, most of these patients already had neutralizing antibodies before the 1st booster, except 4 patients in cohort 2 (gray and red dots **Figure 3**).
- Neutralizing antibody response in ofatumumab treated patients 1 month after 1st booster increased to a comparable level as in control group and as in patients treated with 1st line DMTs or no DMT (**Figure 3A**). 3/4 patients who were seronegative before booster seroconverted during stable ofatumumab treatment (grey dots)
- Within the next 5 months, median levels of neutralizing antibodies decreased in all cohorts with strongest decrease in patients receiving booster vaccination during stable ofatumumab treatment. However, decrease in this cohort was mostly driven by patients already showing low antibody levels at study start (grey and red dots **Figure 3**).
- The 2nd booster increased level of neutralizing antibodies in ofatumumab treated patients again to a comparable level as in the control cohorts.
- One patient in the ofatumumab treated group remained seronegative throughout the trial despite two booster vaccination (red dot).
- T-cell response was comparable between cohorts (**Figure 3B**). Hypothesis: based on observations after initial vaccination, one month after booster vaccination might be too late to detect T-cell response in some patients via ELISpot assay.

Figure 3: Effect of booster vaccination on neutralizing antibody titer



(A) Figure shows titer of neutralizing antibodies for all patients who received at least one booster vaccination; titers of the last visit before the respective booster and 1 month after the respective booster are shown. Individual values are represented by dots and bars show median values, black arrows indicate assay-specific cut-off for seropositivity. *One patient in cohort 1 and one patient in cohort 2 received a booster vaccination but did not attend the visit 1 month after second booster, #Blood sample for one patient in cohort 2 at baseline could not be analyzed due to a technical problem. **(B)** Extent of T-cell response represents the IFN-γ stimulation index. Each dot represents one patient, medians are indicated by horizontal lines. All available values were included in the analysis. *One patient in cohort 1 and one patient in cohort 2 received a booster vaccination but did not attend the visit 1 month after second booster.

SAFETY

- 5 MS relapses occurred during the study (all patients recovered fully; four relapses in cohort 1 and one relapse in cohort 2).
- 18 patients developed COVID-19 infections during the study and all with CTCAE grade mild/medium and complete recovery. Mean duration of infection was similar in both cohorts (**Table 2**).

Table 2. Details on COVID-19 infections

Variable	Cohort 1 – vaccination prior to treatment	Cohort 2 – vaccination during stable treatment	Cohort 3 – Booster vaccination during stable treatment or no treatment
Number of COVID-19 infections*	4	14	6
Mean duration of infections, days [min; max]	10.5 [7; 16]	10.9 [7; 24]	8.2 [7; 10]
CTCAE grade (mild | medium)	3 | 1	4 | 10	6 | 0
Fully recovered	4	14	6
Temporary treatment interruption	0	2	0

* Numbers of COVID19 infections are not comparable between cohorts due to different numbers of enrolled patients (see Table 1) and varying duration of KYRIOS and AMA-VACC studies (12/18 months for KYRIOS cohorts 1&2 vs 6 months for AMA-VACC cohort 3).

CONCLUSIONS

- **T-cell response** was not affected by ofatumumab treatment after initial and booster vaccination.
- **Neutralizing antibody response after initial vaccination** was present but reduced in ofatumumab patients. Data indicate that booster vaccination might further increase neutralizing antibody titers in ofatumumab patients suggesting the **development of immune memory cells** after their initial vaccination.
- **Neutralizing antibody response after booster** was similar in patients boosted before and during stable ofatumumab treatment. After booster, 3/4 previously seronegative patients seroconverted during continuous ofatumumab treatment.
- Results suggest that **booster vaccines** increase immune response in vast majority of ofatumumab treated patients independently of their treatment status during initial vaccination. Antibody levels before start of ofatumumab therapy influence extend and duration of immune response after booster vaccination.
- Mounting of immune response as assessed in this study is in line with clinical data from ALITHIOS[4] regarding **severity and duration of COVID-19 infections** in ofatumumab treated patients: all infections were CTCAE grade mild or moderate with unobtrusive course of disease.

REFERENCES: 1. Sahin et al. Nature 2021; 595:572-577. **2.** Jackson et al. N Engl J Med 2020; 383:1920-1931. **3.** Ziemssen T et al. Ther Adv Neurol Disord. 2022. **4.** Cross et al. Neurologie & Therapie 2022.

ACKNOWLEDGMENTS: This study was sponsored by Novartis Pharma Vertriebs GmbH.

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 AstraZeneca, Biogen, Celgene, Janssen-Cilag, Merck, Novartis, Pathios Therapeutics, Roche, Sanofi, Teva. **Eugen Schlegel** has received research support, consulting fee and Honoria for lectures from Biogen, Lilly, Merck and Novartis. **Veronika E. Winkelmann** and **Lea Leist** are employees of Novartis. Sponsor of this study is the Novartis Pharma Vertriebs GmbH.

Scan this QR code to download a copy Poster

Visit the web at: http://novartis.medicalcongressposters.com/Default.aspx?doc=XXXX