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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. (KYRIOS clinical trial)

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Introduction

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 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], which makes it 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.

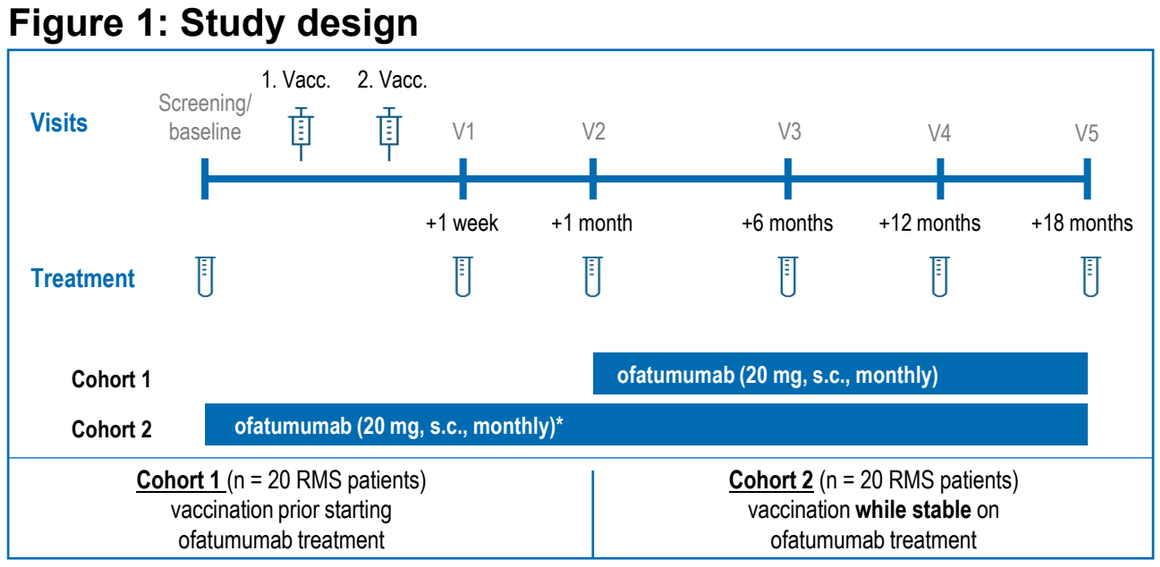
Objective

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

Methods

- KYRIOS is a two-cohort, open-label, prospective study including 40 RMS patients at eight sites in Germany.
  - Cohort 1: patients receive SARS-CoV-2 mRNA vaccination before initiation of ofatumumab treatment
  - Cohort 2: patients receive SRAS-CoV-2 mRNA vaccination during stable ofatumumab treatment (for at least 4 weeks)
- Ofatumumab treatment is administered as part of the study and vaccinations as part of clinical routine according to summary of product characteristics (SmPC).
- This interim analysis focuses on the primary endpoint of the study, which is the proportion of RMS patients having established SARS-CoV-2-specific T cells. Reactive T cells were detected by enzyme-linked immunosorbent spot (ELIspot) assay using the i-Spot Assay-Kit, 3-colour, IFN-γ and IL-2 (ELSP 6110 strip format) kit from GenID® GmbH

Figure 1: Study design



*Vacc.= vaccination with modRNA vaccine according to SmPC; *Ofatumumab treatment needs to be started at least 4 weeks before vaccination.*

Results

Demographics and baseline information

Patient characteristics at the time of screening are shown in **Table 1**.

- There are currently 8 patients enrolled in the study with an average age of 31.5 years and a disease history of 6,2 months.
- All patients in cohort 2, and 4 out of 5 patients in cohort 1 were treatment naive.

Table 1: Patient Characteristics

	Cohort 1 (N=5)	Cohort 2 (N=3)
Age (years)	32.8 [23; 42]	29.33 [21; 39]
Gender, female, N (%)	4 (80)	2 (66)
Time since diagnosis (years)	0.1 [0.1; 0.1]	0.76 [0.1; 3.2]
Prior treatments		
• Naive, N (%)	4 (80)	3 (100)
• One, N (%)	1 (20)	0 (0)

If not indicated otherwise, data are presented as mean [min; max]

SARS-CoV-2 vaccination

- All patients received BioNTech/Pfizer SARS-CoV-2 mRNA vaccines with an average of 21.9 days between 1st and 2nd dose.
- B cell depletion was verified in al subjects of cohort 2 at the time of vaccination.
- At the time of this first interim analysis, T cell data on V1 were available for n=4 and n=1 from cohort 1 and 2, respectively.

Table 2: Summary of SARS-CoV-2 vaccines

	Cohort 1 (N=5)	Cohort 2 (N=3)
Type		
• BioNTech/Pfizer, N (%)	5 (100)	3 (100)
• Moderna, N (%)	-	-
Time between vaccines (days)	21 [21; 21]	24.5 [21; 28]
Therapy at time of vaccine		
• Yes, N (%)	-	3 (100) (Ofatumumab)
• No, N (%)	5 (100)	-
CD19+/CD20+ cells at baseline (cells/µl)	232.3 [53.8; 452.9]	0
T-cell response* (1 week, V1)		
- Absent, N (%)	-	-
- Present, N (%)	4 (100)	1 (100)
T-cell response* (4 weeks, V2)		
- Absent, N (%)	-	-
- Present, N (%)	1 (100)	1 (100)

**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. All patients that passed the respective time points were included in the analysis. If not indicated otherwise, data are presented as mean [min; max]*

Conclusions

- Patients in this study represent a young cohort at an early stage of their disease.
- For the one patient on stable Ofatumumab, SARS-CoV-2 specific T-cells were detected 1 week and 1 month after vaccination. This observation is consistent with a recent publication showing development of SARS-CoV-2 specific T-cells following vaccination in patients with MS treated with other anti-CD20 therapies[3].
- This study is ongoing and will provide data on the presence and maintenance of T-cell response over time as well as the development of SARS-CoV-2 specific antibodies and the effect of booster vaccines. The present interim data indicate that both humoral and cellular response need to be considered for interpretation of vaccination efficacy.

References

[1]Sahin et al.(2021), *Nature.* 595,572–577; [2]Jackson et al. (2020), *N Engl J Med.* 383:1920-1931; [3]Apostolidis et al. (2021), *Nature Medicine*.

Disclosures

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