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)

Tjalf Ziemssen1, Tobias Bopp2, Benjamin Ettle3, Marie Groth3
1Center of Clinical Neuroscience, Dresden University of Technology, Dresden, Germany; 2Institute for Immunology, University Medical Center, Mainz, Germany; 3Novartis Pharma GmbH, Nuremberg, Germany

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 responses1,2, 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.

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

<table>
<thead>
<tr>
<th>Cohort 1 (N=5)</th>
<th>Cohort 2 (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.8 [23; 42]</td>
</tr>
<tr>
<td>Gender, female, N (%)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>0.1 [0.1; 0.1]</td>
</tr>
<tr>
<td>Prior treatments</td>
<td></td>
</tr>
<tr>
<td>- None, N (%)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>T-cell response* (4 weeks, V2)</td>
<td></td>
</tr>
<tr>
<td>- Present, N (%)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>- Absent, N (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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 all 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

<table>
<thead>
<tr>
<th>Cohort 1 (N=5)</th>
<th>Cohort 2 (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>- BioNTech/Pfizer, N (%)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Time between vaccines (days)</td>
<td>21 [21; 21]</td>
</tr>
</tbody>
</table>

T-cell response measured by secretion of INF-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 therapies3.
• 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
1Sahin et al.(2021), Nature 583:1920-1931; 3Apostolidis et al. (2021), Nature Medicine
2Nature Medicine
3Celgene, Merck, Novartis, Pathios Therapeutics, Roche, Teva.

Disclosures
T2 has received research support, consulting fee and honoraria for lectures from Alexion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, Teva.
TB has received consulting fee and honoraria for lectures from Biogen, Celgene, Merck, Novartis, Pathios Therapeutics, Roche, Teva.
BE and MG are employees of Novartis.

Poster presented at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), virtual congress, 13th - 15th October 2021.
This study was sponsored by Novartis Pharma Vertriebs GmbH.

Figure 1: Study design

Table: Summary of SARS-CoV-2 vaccines

<table>
<thead>
<tr>
<th>Type</th>
<th>Cohort 1 (N=5)</th>
<th>Cohort 2 (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- BioNTech/Pfizer, N (%)</td>
<td>5 (100)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>- Moderna, N (%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time between vaccines (days)</td>
<td>21 [21; 21]</td>
<td>24.5 [21; 28]</td>
</tr>
</tbody>
</table>

T-cell response measured by secretion of INF-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 therapies3.
• 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

Disclosures
T2 has received research support, consulting fee and honoraria for lectures from Alexion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, Teva.
TB has received consulting fee and honoraria for lectures from Biogen, Celgene, Merck, Novartis, Pathios Therapeutics, Roche, Teva.
BE and MG are employees of Novartis.

Poster presented at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), virtual congress, 13th - 15th October 2021.
This study was sponsored by Novartis Pharma Vertriebs GmbH.