Assessing the immune response to SARS-CoV-2 mRNA vaccines in patients with secondary progressive multiple sclerosis treated with siponimod (AMA-VACC clinical trial)

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Introduction

SARS-CoV-2 mRNA vaccines are a key factor in the fight against the COVID-19 pandemic across the globe. However, to date limited data is available on the immune response to this novel class of vaccines with concomitant immunomodulatory treatments which could affect the immune response[1,2]. Siponimod is a highly selective $S1P_1$ and $S1P_5$ receptor modulator authorized by the EMA for the treatment of secondary progressive multiple sclerosis (SPMS) with active disease. One key mode of action for siponimod is the sequestration of T-cells to the lymph nodes[3]. As both humoral and cellular immune responses play an important role in vaccinations it is essential to investigate not only the antibody response but also the effect on T-cells especially in a T-cell targeting therapy such as siponimod. With this data on SARS-CoV-2 vaccinations in the vulnerable population of siponimod treated SPMS patients we hope to offer a vaccination guidance to treating physicians and patients.

Objective

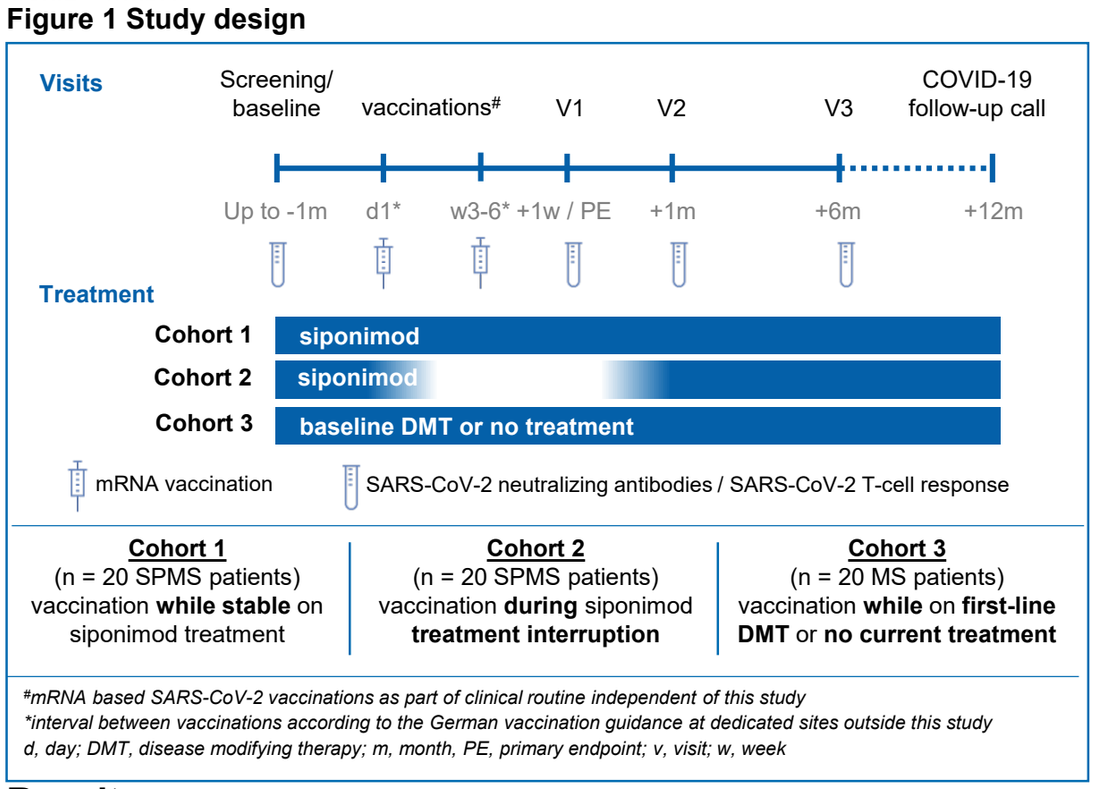
With this first interim analysis we are aiming to characterize the immune response in siponimod treated SPMS patients one week after a complete cycle of a SARS-CoV-2 mRNA vaccination.

Methods

AMA-VACC[4] is a clinical open-label, three-cohort, prospective study with currently 41 MS patients enrolled in Germany. (SP)MS patients treated with siponimod or a first line DMT (glatirameracetate, dimethylfumarate, interferons, teriflunomide) or no current therapy as part of clinical routine were eligible to participate if there was no sign of an acute (PCR) or previous (IgG or IgA) SARS-CoV-2 infection. Participants received the SARS-CoV-2 mRNA vaccinations as part of clinical routine, independent of this study (**Figure 1**).

Neutralizing antibodies were detected utilizing the cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit from GenScript USA Inc (L00847) and SARS-CoV-2 specific T-cells were detected with the CoV-iSpot Interferon-γ + Interleukin-2 (ELSP 7010 strip format) from GenID® GmbH.

Figure 1 Study design



#mRNA based SARS-CoV-2 vaccinations as part of clinical routine independent of this study
**interval between vaccinations according to the German vaccination guidance at dedicated sites outside this study*
d, day; DMT, disease modifying therapy; m, month, PE, primary endpoint; v, visit; w, week

Results

Demographics and baseline information

Patient characteristics at screening for this first interim analysis are depicted in **Table 1**.

Table 1 Patient characteristics

Variable*	Cohort 1 – siponimod continuously	Cohort 2 – siponimod interrupted for vaccination	Cohort 3 – first line DMT / no current treatment
N	17	4	20
Age, years	56 [42; 66]	56 [53; 58]	51 [22; 71]
Sex, female, n (%)	13 (76.5)	3 (75.0)	16 (80.0)
MS diagnosis, n (%)			
SPMS, active SPMS	17 (100.0)	4 (100.0)	2 (10.0)
RRMS, active RRMS	-	-	12 (60.0)
MS, not specified	-	-	6 (30.0)
Time since first MS diagnosis, years	15.06 [5.4; 30.9]	17.60 [3.4; 25.0]	9.13 [3.2; 37.9]
MS treatment, n (%)			
Siponimod	17 (100.0)	4 (100.0)	-
Glatirameracetate	-		6 (30.0)
Interferon	-		3 (15.0)
Teriflunomide	-		7 (35.0)
No current therapy	-		4 (20.0)
Time on current treatment, years	0.63 [0.1; 0.9]	0.34 [0.2; 0.5]	4.33 [2.8; 22.1]
Vaccination, n (%)			
1st (BioNTech | Moderna)	16 (94.1) | 1 (5.9)	4 (100.0) | -	19 (95.0) | 1 (5.0)
2nd (BioNTech | Moderna)	16 (94.1) | 1 (5.9)	4 (100.0) | -	18 (90.0) | 1 (5.0)
Vaccination time interval (days)			
1st to 2nd vaccination	41.0 [21; 42]	36.5 [21; 42]	42.0 [21; 47]
2nd vaccination to Visit 1	7.0 [6; 10]	6.0 [6; 10]	7.0 [6; 10]

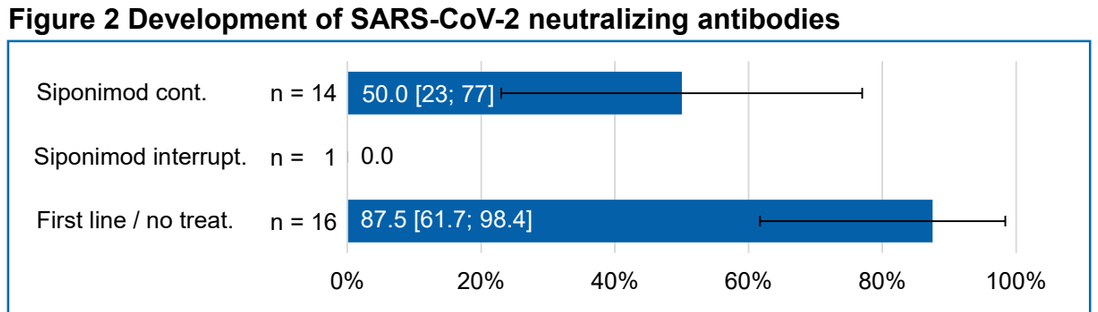
** if not indicated otherwise, data are presented as median [min; max]*

At the time of this interim analysis, 17, 4, and 20 patients were recruited into cohort 1, 2, and 3, respectively. Participants were of advanced age (51 - 56 years) with a long MS history, especially in the SPMS cohorts (15-17 years). 95% of primary and 93% of secondary mRNA SARS-CoV-2 vaccinations in this study were form Biontech/Pfizer.
At baseline all patients were tested negative for a previous or acute SARS-CoV-2 infection by assessing IgA (≤ 0.8 Index) and IgG (≤ 50 AU/ml) levels and a PCR test.

Development of SARS-CoV-2 neutralizing antibodies

The primary endpoint of this study is the proportion of patients achieving seroconversion, i.e. development of SARS-CoV-2 neutralizing antibodies one week after 2nd vaccination. **Figure 2** shows a seroconversion rate of 50% in patients continuously treated with siponimod and of 88% in cohort 3 patients. The two patients not achieving seroconversion in the latter cohort were treated with teriflunomide which corresponds to 40% non-responders for teriflunomide.

Figure 2 Development of SARS-CoV-2 neutralizing antibodies

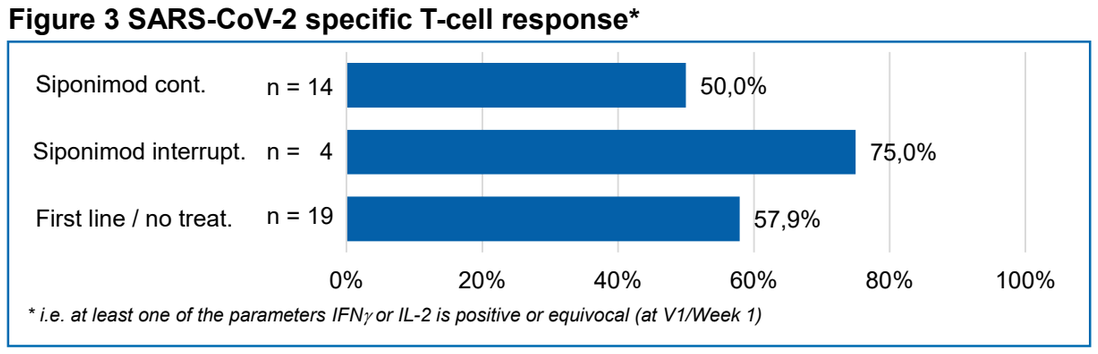


Bars indicate exact two sided confidence intervals according to Clopper-Pearson.

SARS-CoV-2 specific T-cell response

SARS-CoV-2 specific T-cell response was assessed by EliSpot measuring the release of Interleukin-2 (IL-2) or interferon gamma (IFN-γ) by CD3+ T-cells upon antigen stimulation (**Figure 3**).

Figure 3 SARS-CoV-2 specific T-cell response*



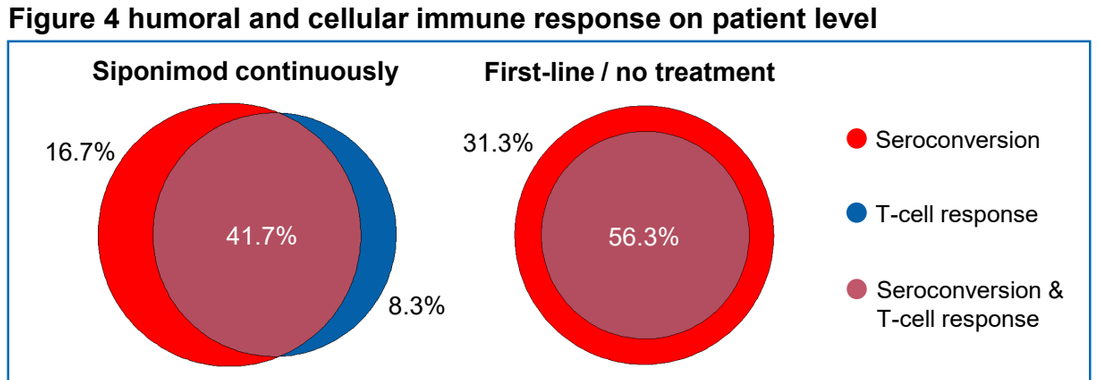
** i.e. at least one of the parameters IFNγ or IL-2 is positive or equivocal (at V1/Week 1)*

50% of patients continuously treated with siponimod mounted a T-cell response 1 week past full vaccination. 75% of patients interrupting their treatment were found to have a positive T-cell response. However, numbers are low in this cohort.
T-cell responses in cohort 3 gave a mixed picture: 3 (100%) interferons, 4 (67%) teriflunomide, 3 (50%) glatirameracetate, and 1 (30%) patient with no current treatment showed a positive T-cell response.

Combined immune response

Importantly, **Figure 4** depicts that not all patients with an immune response were positive for both humoral and cellular systems at this early point past vaccination.

Figure 4 humoral and cellular immune response on patient level



Note: Data presented are for patients with evaluable antibody and T-cell assessments
Number of evaluable patients (N): Siponimod continuously: N = 12; First-line / no treatment N = 16
Patients with no response (n [%]): Siponimod continuously : n = 4 [33.3%]; First-line / no treatment n = 2 [12.5%]

Taken together, 66% of patients with continuous siponimod treatment have mounted an immune response (i.e. humoral and/or cellular response) to SARS-CoV-2 mRNA vaccinations after 1 week.

Safety

No relapses occurred and no clinical significant findings were observed until the cut-off date of this interim analysis. No COVID-19 infection was reported and no adverse events led to permanent discontinuation of study medication. Overall, safety results were in agreement with previous safety data, both for MS DMTs and vaccines.

Conclusions

- In a population older than 56 in median and with a long MS history, the first interim analysis of AMA-VACC shows that nearly 2 out of 3 patients with SPMS on siponimod develop an immune response to SARS-CoV-2 mRNA vaccines. Overall this is in line with previous vaccination studies in S1P modulators[5,6] and recent publications recommending SARS-CoV-2 vaccinations also for MS patients receiving DMTs[2,7,8].
- Data suggests that both humoral and cellular immune response need to be considered when assessing the vaccination as also pointed out by others[9]
- Further analyses are required at one and six months past vaccination and also including possible booster vaccinations in this comparably small study to follow up on the long-term effects. However, first results let us expect a further increase of humoral immune responses compared to one week after vaccination.

References

1. Negahdaripour et al. (2021) Int Immunopharmacol 99:108021.
2. Bigaut et al. (2021) Neurol Neuroimmunol Neuroinflamm. 8(5):e1055
3. Behrangi et al. (2019) Cells. 7;8(1):24
4. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-005752-38/DE
5. Ufer et al. (2017) Neurol Neuroimmunol Neuroinflamm. 4(6):e398
6. Kappos et al. (2015) Neurology. 84(9):872-9
7. Korsukewitz et al. (2021) Nat Rev Neurol. 17(4):260
8. Centozone et al. (2021) J Neurol. 12;1-8
9. Woopen et al. (2021) Front. Immunol. 12:701752

Disclosures

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