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COVID-19 Outcomes and Seropositivity Rates Following SARS-CoV-2 Vaccine and/or Infection in Ofatumumab-Treated RMS Patients: Data From the ALITHIOS Open-Label Extension Study

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SUMMARY

1. Most COVID-19 cases in patients with relapsing multiple sclerosis (RMS) receiving ofatumumab in ALITHIOS were non-serious and mild to moderate in severity, and most patients recovered
   - There was no evidence of an association between the seriousness of COVID-19 cases and ofatumumab exposure[1]
2. The serological response to SARS-CoV-2 vaccines was evaluated retrospectively in RMS patients receiving ofatumumab in the ongoing ALITHIOS open-label extension study
   - Patients with multiple immunisation/exposure events (i.e. patients who received at least 1 booster vaccination or had COVID-19 after being fully vaccinated) had the highest rates of seropositivity
   - No association was observed between the duration of ofatumumab treatment and serological responses

INTRODUCTION

- SARS-CoV-2 vaccines played a key role in fighting the pandemic by protecting individuals from SARS-CoV-2 infection and developing (serious) COVID-19
- Anti-CD20 therapies have been associated with an attenuation of humoral immune responses to SARS-CoV-2 infection or vaccination[2-5]; however, it has been previously shown that anti-CD20 treatment, including ofatumumab, does not prevent T-cell reactivity towards SARS-CoV-2[4,6,7]
- However, no robust data are available on the serological response to SARS-CoV-2 vaccines in patients with RMS

OBJECTIVE

- To evaluate COVID-19 outcomes and the serological response to SARS-CoV-2 vaccination and/or infection in patients with RMS receiving ofatumumab

METHODS

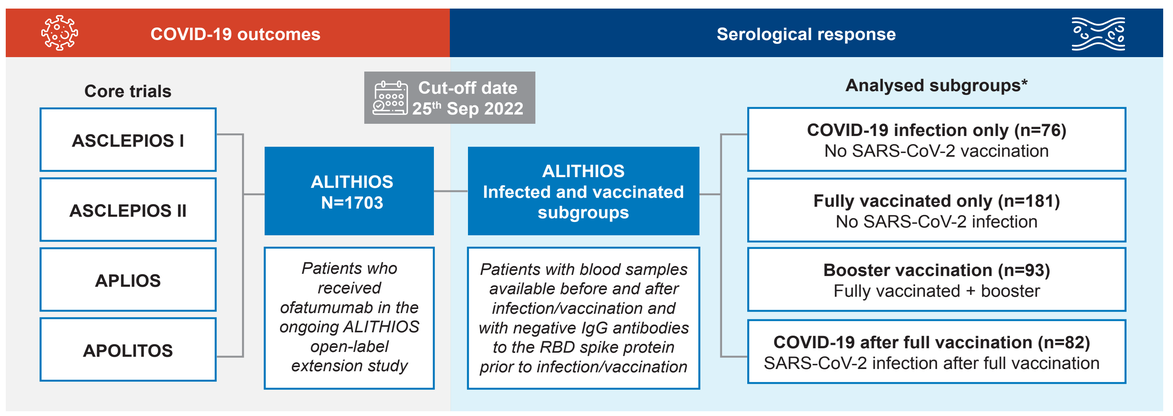
COVID-19 OUTCOMES

- COVID-19 outcomes were evaluated in patients with RMS (N=1703) receiving ofatumumab in the ongoing ALITHIOS open-label extension study (data cut-off: 25th Sep 2022; **Figure 1**)

SEROLOGICAL RESPONSE

- This post-hoc analysis retrospectively evaluated the serological response to SARS-CoV-2 vaccines/infection in:
  - A subset of patients from ALITHIOS who had COVID-19 and/or vaccination, based on the number of immunisation/exposure events (an event could be an infection or a vaccination)
    - A subgroup of the above subset, categorised into four subgroups as outlined in **Figure 1**
- Antibody levels to the receptor-binding domain (RBD) spike protein were measured using the Abbott Architect SARS-CoV-2 IgG II Quant assay (antibody units [AU] were converted to binding antibody units [BAU]; [BAU/mL = 0.142 × AU/mL] and the seropositivity level was set at 7.1 BAU/mL [50 AU/mL])

Figure 1. Study Design and Patient Population



*a patient may have contributed to more than one subgroups analysed; RBD, receptor-binding domain.

- Demographic and treatment characteristics were compared between patients who were seropositive following immunisation/exposure events (responders to infection and/or vaccination) and those with no antibody response (non-responders)
- Age, gender, duration of ofatumumab treatment, time since the last ofatumumab injection, vaccination/infection status, time since the last immunisation/exposure event (infection or vaccination) were evaluated to assess their effect on the serological response
  - To assess the effects of these factors, a logistic regression model was fit for seropositivity (Yes/No) and a linear model was used for continuous SARS-CoV-2 IgG antibody levels

RESULTS

COVID-19 OUTCOMES[1]

- As of 25 Sep 2022, 38% (648/1703) of ofatumumab-treated patients who entered ALITHIOS (mean age at baseline: 39.2 years; women, 69.6%; body mass index [BMI] ≥30 kg/m^2, 18%) reported COVID-19 (confirmed, n=603; suspected, n=45)
- The outcomes of these cases are summarised in **Table 1**

Table 1. COVID-19 Outcomes

Parameter	Outcome
Severity	Mild to moderate: **93.9%**
Seriousness	Non-serious: **92.3%**; Serious: **7.7%**
Recovery	Recovered: **96.1%**; recovered with sequelae: **1.9%**; recovering: **0.6%**
Deaths	**5** patients (3 were unvaccinated, 2 were fully vaccinated[a])
Treatment interruption	No treatment interruption: **87.5%**
Treatment discontinuation	**5** patients discontinued ofatumumab due to COVID-19 or COVID-19 pneumonia; these discontinuations represent the 5 fatalities noted above
Re-infection	**3.8%** had a COVID-19 reinfection (at the onset of re-infection: 26 unvaccinated, 4 partially vaccinated, 22 fully vaccinated, 10 had received booster doses, and 2 had received ≥2 booster doses)
COVID-19 after full vaccination	**167/705** reported COVID-19, reported mostly when Omicron variant was dominant

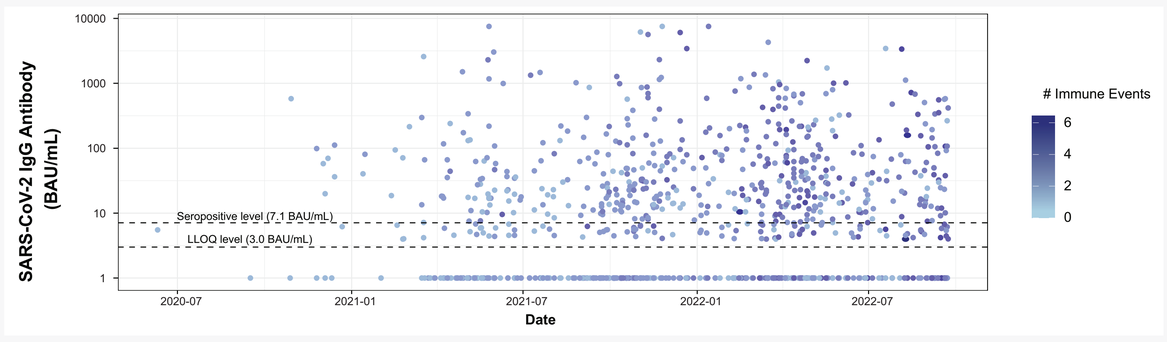
[a]These two fatal outcomes occurred before a booster dose, one case had multiple risk factors for severe COVID-19 and the other case was complicated by a bilateral pneumothorax.

- The identified risk factors for serious COVID-19 were male sex and a high BMI (≥30 kg/m^2 vs <30 kg/m^2); duration of ofatumumab exposure was not associated with an increased risk of serious COVID-19

SEROLOGICAL RESPONSE

- Anti-RBD antibody levels in patients with RMS with multiple SARS-CoV-2 exposures (infection or vaccination) are presented in **Figure 2**

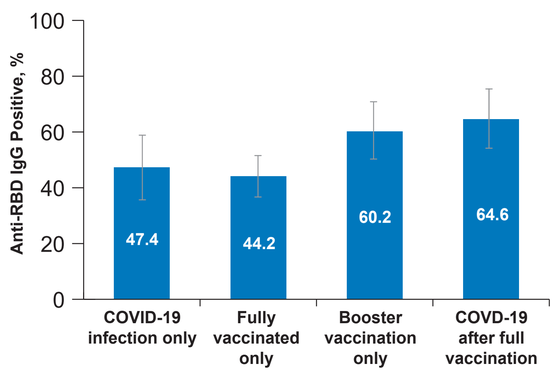
Figure 2. SARS-CoV-2 Anti-RBD Antibody Levels Over Time by Number of Immunisation/Exposure Events



Each exposure to SARS-CoV-2 (infection or vaccination) was counted as an event.
BAU, binding antibody units; IgG, immunoglobulin G; LLOQ, lower limit of quantification; RBD, receptor-binding domain; SD, standard deviation.

- A serological response was observed in all four subgroups of vaccination/infection status, and was more prominent in patients with COVID-19 after full vaccination and in those who received booster vaccination (**Figure 3**)

Figure 3. Seropositivity Rates Across Subgroups



	Anti-RBD IgG concentration, (BAU/mL)	
	Geometric mean±SD	Median (Range) (min-max)
COVID-19 Infection only	8.19 (±7.57)	5.82 (1.0–6159.9)
Fully vaccinated only	6.43 (±7.86)	4.49 (1.0–1503.3)
Booster vaccination only	17.54 (±10.57)	23.69 (1.0–5657.6)
COVD-19 after full vaccination	17.82 (±10.89)	16.33 (1.0–6059.8)

BAU, binding antibody units; IgG, immunoglobulin G; RBD, receptor-binding domain; SD, standard deviation.

FACTORS AFFECTING SEROLOGICAL RESPONSE

- COVID-19, COVID-19 after full vaccination, receipt of ≥1 booster dose and male gender were associated with increased seropositivity rates ($p<0.05$ for all)
- The duration of ofatumumab treatment was not associated with the serological response

CONCLUSIONS

- Most COVID-19 cases in RMS patients receiving ofatumumab in ALITHIOS were non-serious, mild-to-moderate in severity, and most patients recovered without sequelae
- Serological responses were detected after both SARS-CoV-2 infection and vaccination in patients with RMS treated with ofatumumab
- A booster vaccination increased the seropositivity rate relative to the initial vaccination
- Patients with COVID-19 after full vaccination had higher seropositivity rates than unvaccinated patients when infected with COVID-19, suggesting that a high number of immune stimulations may play a key role in developing a robust humoral response[8]
- The duration of ofatumumab treatment had no association with serological responses
- Anti-RBD IgG seropositivity rates and antibody response levels reported here are in line with previous reports for ofatumumab[6]
- The innate and T-cell responses to immunisation are also critical parts of the immune response against SARS-CoV-2; however, these aspects of the response were not investigated in these post-hoc analyses because peripheral blood mononuclear cells required for such analyses were not available

References: 1. Wiendl H, et al. ePresentation at *EAN* 2023: EPR-303; **2**. Jeantin L, et al. *J Neurol Neurosurg Psychiatry*. 2023;0:1–10; **3.** Brill L, et al. *JAMA Neurol*. 2021;78:1510–4; **4.** Alfonso-Dunn R, et al. *Front Immunol*. 2023:28;14:1194671; **5.** Achiron A, et al. *Ther Adv Neurol Disord*. 2021:14:17562864211012835; **6.** Ziemssen T, et al. *Vaccines (Basel)*. 2023; 11(5):978; **7.** Faissner S, et al. *Front Immunol*. 2022;12:980526; **8.** Stoll S, et al. *Mult Scler Relat Disord*. 2023;71:104574.

Abbreviations: **BAU**, binding antibody units; **IgG**, immunoglobulin G; **LLOQ**, lower limit of quantification; **RBD**, receptor-binding domain; **RMS**, relapsing multiple sclerosis; **SD**, standard deviation.

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