Antibody Response After Initial Vaccination for SARS-CoV-2 in Patients With Amyloidosis

Efstathios Kastritis¹, Evangelos Terpos¹, Aimilia Sklirou², Foteini Theodorakakou¹, Despina Fotiou¹, Eleni-Dimitra Papanagnostou², Tina Bagratuni¹, Nikolaos Kanellias¹, Maria Gavriatopoulou¹, Ioannis P. Trougakos², Meletios A. Dimopoulos¹

Correspondence: Efstathios Kastritis (ekastritis@med.uoa.gr).

In systemic amyloidoses, misfolded proteins form amyloid fibrils that are deposited in various tissues causing organ dysfunction. In systemic immunoglobulin light chain (AL) amyloidosis, a usually small plasma cell clone produces a monoclonal immunoglobulin light chain with amyloidogenic properties. Although modest in size, this plasma cell clone may affect immunocompetence, while organ dysfunction further increases susceptibility and risk of complications of infectious diseases. In addition, the use of anti-plasma cell therapies further decreases the fitness of the immune system. Thus, COVID-19 is particularly challenging for patients with critical organ involvement by amyloidosis.¹² Vaccination against SARS-CoV-2 is the best strategy to avoid severe COVID-19, however, response to vaccines may be compromised in patients with plasma cell malignancies or other B-cell lymphoproliferative disorders.³⁴ In patients with ATTR such a clone does not exist, but other factors could affect response to vaccination. Since it is clinically relevant to evaluate the efficacy of anti-SARS-CoV-2 vaccination in patients with AL and ATTR amyloidosis, to optimize strategies for the immunization of this vulnerable patient population, we measured the titers of neutralizing antibodies (NAbs) against SARS-CoV-2 after the first dose of the BNT162b2 and AZD1222 vaccines.

This report is part of larger prospective study (NCT04743388) for the kinetics of anti-SARS-CoV-2 antibodies after COVID-19 vaccination. The major inclusion criteria for this analysis include: (1) a prior diagnosis of AL or ATTR amyloidosis; (2) vaccination for vaccination. As a control group we used volunteers matched for age, gender (1:3) who had (1) no autoimmune or active malignant disease; (2) no HIV or active hepatitis B and C infection. Serum was separated within 4 hours from blood collection and stored at −80°C until the day of measurement on (1) day 1 (D1; before the first dose of BNT162b2 or AZD1222) and (2) day 22 (D22; before the second dose of the BNT162b2 or 3 weeks after the first dose of AZD1222). NAbs against SARS-CoV-2 were measured using FDA-approved methodology (ELISA, cPass SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ).³ The study was approved by the respective Ethical Committees in accordance with the Declaration of Helsinki and all patients and controls provided written informed consent before enrollment.

Our study included 59 patients with AL amyloidosis (34 males/25 females; median age: 62, interquartile range [IQR]: 57–72 years) and 118 controls (68 males/50 females; median age: 62, IQR: 57–72 years), who were vaccinated during the same period, at Alexandra Hospital, Athens, Greece. The patients followed a centrally controlled vaccination program run by the Greek healthcare authorities that prioritized healthcare workers, the elderly and patients with malignancies for anti-SARS-CoV-2 vaccination (with either BNT162b2 or AZD1222). The proportion of the different vaccines was similar in patient and control groups (78% had BNT162b2 and 22% had AZD1222, respectively). At the time of vaccination, 31/59 (53%) patients were receiving anti-clonal therapy, Table 1 shows the other characteristics of the patients.

Table 1. Characteristics of the Patients With AL Amyloidosis Who Were Included in the Analysis.

| Male/Female | 34 (58%)/25 (42%) |
| Age, median (range) | 62 (35–86) |
| BNT162b2 | 46 (78%) |
| AZD1222 | 13 (22%) |
| Renal involvement | 41 (69%) |
| Heart involvement | 38 (64%) |
| Liver involvement | 7 (12%) |
| PNS/ANS involvement | 11 (19%) |
| Mayo stage 1/2/3 | 22%/51% /27% |
| Bone marrow plasma cells at diagnosis | 10% (0–30%) |
| eGFR (mL/min/1.73 m²) | 77 (9–150) |
| On active treatment at the time of vaccination | 31 (53%) |
| Therapies (prior/current) |  
| Bortezomib or Ixazomib | 41 (69%)/13 (22%) |
| Daratumumab | 16 (27%)/11 (19%) |
| Lenalidomide | 6 (10%)/3 (9%) |
| Cyclophosphamide | 37 (63%)/13 (22%) |
| Prior ASCT | 4 (7%) |
| Disease in hematologic remission (CR or VGPR) | 44 (75%) |

ANSA = autonomic nervous system; AL = immunoglobulin light chain; ASCT = autologous stem cell transplantation; CR = complete response; eGFR = estimated glomerular filtration rate; PAS = peripheral nervous system; VGPR = very good partial response.
At baseline, before the first vaccine shot (ie, on D1), only 5 (8%) patients and 14 (12%) controls had NAb titers of ≥30% (positivity cutoff) and there was no significant difference of the NAb titers between patients and controls (median 11.95% versus 15.2%, P = 0.831). Four patients with AL had baseline NAb titers above 50%, of which only 2 reported a history of COVID-19 infection.

On day 22 after the first dose, there was a significant increase in the levels of NAbs in controls (paired t-test, P < 0.001) as well as in those with AL amyloidosis (paired t-test, P = 0.0027); however, the median NAb titers for AL patients was 22.9% (range 0.5%–97.98%) compared to 44.9% (range 1.8%–98.3%) in controls (P < 0.001), so that 25/59 (42.4%) versus 78.5% developed NAb titers ≥30% (P < 0.001) (Figure 1A) and 14/59 (23.7%) AL patients versus 44% controls (P = 0.008) developed NAb titers ≥50% (which is the clinically relevant threshold for viral inhibition5). NAbs on D22 were similar for BNT162b2 and AZD1222.

Among the 14 patients with AL amyloidosis and NAbs >50% at D22, 12 received BNT162b2, and 2 received AZD1222, 11/14 had clonal disease in deep remission (hematologic complete response or very good partial response) and 4 patients were still on treatment: 1 with ixazomib/dexamethasone, 1 with lenalidomide/dexamethasone, 1 with VCD (and prior history of COVID), and 1 with daratumumab. Among the other 10 patients, 7 had prior treatment with daratumumab in their most recent line of therapy that was discontinued at least 6 months ago (1 had also a prior history of COVID-19 infection). We also compared NAb titers among those on therapy and those being at least 3 months post-therapy (matched NAb titers were 33.4% (range 14.3–55.7) versus 19.8% (range 0.5%–77.4%) (P = 0.083) (Figure 1B). We found no significant differences in NAb titers between patients and controls (median 11.95% versus 15.2%, P = 0.831). Four patients with AL had baseline NAb titers above 50%, of which only 2 reported a history of COVID-19 infection.

To the best of our knowledge, this is the first data on the humoral response after vaccination for SARS-CoV-2 in patients with AL and ATTR amyloidosis. Compared to a matched control population, patients with AL amyloidosis develop lower level of NAbs, corresponding to a less intense response of their adaptive humoral immunity, despite the low tumor burden. The immunosuppressive role of the underlying plasma cell clone in patients with AL amyloidosis (although tumor burden is low) is critical and these results are not significantly different from data in patients with myeloma (published from our group6 and others7). Patients with amyloidosis but no clonal disease (ie, those with ATTR) developed NAbs response similar to their matched controls. We also observed that anti-clonal therapy during the period of vaccination may affect humoral response. Although it is recommended that a treatment-free period should precede and follow vaccination, this may not be feasible: vaccination is an urgent need for those most vulnerable but, it may not be possible to hold treatment for a disease like AL amyloidosis. Nevertheless, patients on therapy who are in deep hematologic remission may still mount adequate NAbs titers. Interestingly, 4 “responders” had prior use of daratumumab, an anti-CD38 monoclonal antibody targeting the plasma cell compartment. However, to optimize immunization strategies, the timing of vaccination and the role of concomitant therapy requires further investigation. At this point, with still a limited number of patients, we found no correlations between patient characteristics and response. The impact of therapy or a specific therapy needs to be further evaluated and may change with larger numbers of patients or after the second dose or after longer follow up. Importantly, although the numbers are small, NAbs responses are similar for both BNT162b2 and AZD1222.

A significant proportion of the control group did not develop Nabs >50% at D22, but it is known that after the second dose (at least for BNT162b2) a substantial proportion develops very high titers, even among the elderly.8 Responses were also less robust in the very elderly, which includes most patients with ATTRwt. Thus, a second vaccine dose should always be given in patients with AL amyloidosis (and probably other lymphoproliferative disorders or with immunosuppression) as well as the elderly8 to increase the probability of adequate humoral response to vaccination. In conclusion, patients with AL amyloidosis have a less robust response to anti-SARS-CoV-2 vaccination after the first dose compared to matched controls; a second dose is necessary and perhaps additional booster doses may be needed (or use of different vaccine) in those not mounting an adequate humoral response.

Figure 1. (A) Kinetics of neutralizing antibodies (NAbs) in patients with AL amyloidosis and age and sex-matched controls before and after the first vaccination dose for SARS-CoV-2 (with BNT162b2 or AZD1222 vaccine). (B) Kinetics of neutralizing antibodies (NAbs) in patients with AL amyloidosis on active therapy vs those not currently receiving anti-clonal therapy. AL = immunoglobulin light chain.

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**Disclosures**

The authors have no conflicts of interest to disclose.

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