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#### AUTHOR CONTRIBUTIONS

Tycel Phillips and Jamie Hirata contributed to the conception and design of the study; Mark Brunvand contributed to the conception, design, data collection, and data analysis; Tycel Phillips, Andy I. Chen, James Essell, Catherine Diefenbach, David Ramies, Jamie Hirata, and Ian W. Flinn contributed to the collection and assembly of data, and data analysis/interpretation; Annalisa Chiappella and Franck Morschhauser contributed to data analysis and interpretation; Tycel Phillips, Andy I. Chen, James Essell, Annalisa Chiappella, and Catherine Diefenbach contributed to the treatment of study patients; Ji Cheng contributed to the statistical analysis and interpretation of the clinical data.

#### DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are available here (<https://vivli.org/members/ourmembers/>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: ([https://www.roche.com/research\\_and\\_development/who\\_we\\_are\\_how\\_we\\_work/clinical\\_trials/our\\_commitment\\_to\\_data\\_sharing.htm](https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)).

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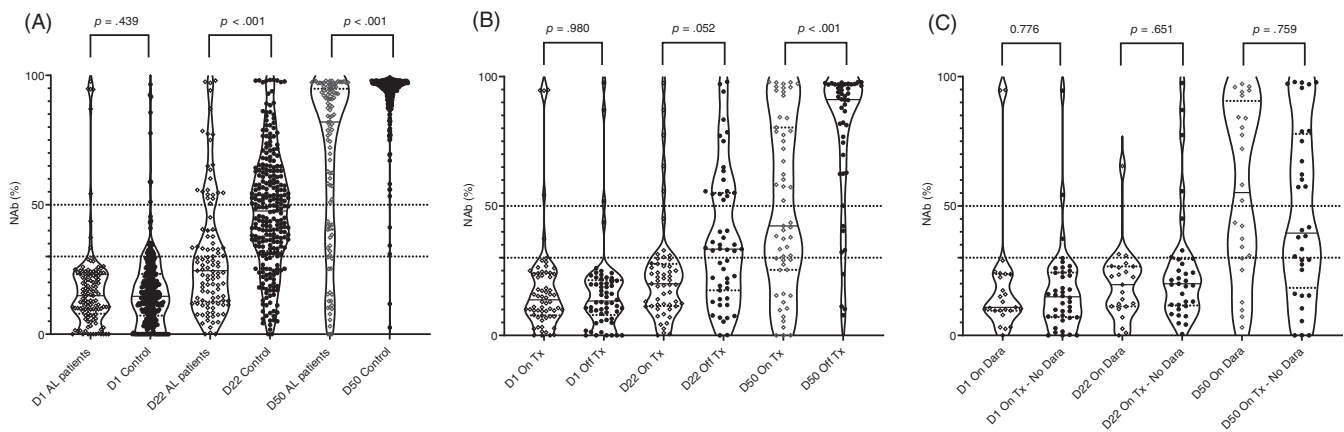
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# Kinetics of anti-SARS-CoV-2 neutralizing antibodies development after BNT162b2 vaccination in patients with amyloidosis and the impact of therapy



**FIGURE 1** (A) Kinetics of neutralizing antibodies (NAbs) in patients with AL amyloidosis and age and sex-matched controls before and after the vaccination with BNT162b2. (B) Kinetics of neutralizing antibodies (NAbs) in patients with AL amyloidosis on active therapy (On Tx) versus those not currently receiving anti-clonal therapy (Off Tx). (C) Kinetics of neutralizing antibodies (NAbs) in patients with AL amyloidosis on active treatment with daratumumab (On Dara) or on active treatment that does not contain daratumumab (On Tx—No Dara)

To the Editor:

Systemic light chain (AL) amyloidosis is caused by a usually small plasma cell clone that produces amyloidogenic immunoglobulin light chains. This clone may affect immune competence and immune system fitness but, in addition, organ dysfunction, leading to heart failure, nephrotic range proteinuria, malabsorption, etc. further increases susceptibility to infections and risk of complications. Anti-plasma cell therapies cause immunosuppression and have been associated with increased risk of infectious complications, including COVID-19.<sup>1,2</sup> Vaccination against Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the best strategy to avoid severe Coronavirus disease 2019 (COVID-19),<sup>3</sup> however, response to vaccines is compromised in patients with plasma cell malignancies or other B-cell lymphoproliferative disorders.<sup>4–8</sup>

Data on the humoral responses to vaccination against COVID-19, for patients with AL amyloidosis is limited. Subjects with asymptomatic plasma cell dyscrasias (monoclonal gammopathy of undetermined significance [MGUS] or smoldering myeloma) may have attenuated responses to vaccination,<sup>6</sup> but although the clones in these patients may be similar in extent to the plasma cell clone in AL amyloidosis, these patients are not receiving active therapy. We reported that after the first dose of vaccine in 59 patients with AL amyloidosis, there was a blunted humoral response; but results following the second dose of the vaccine were not available.<sup>9</sup> We also observed that patients with transthyretin-related amyloidosis (ATTR<sup>w/t</sup>), despite their old age could mount a post-vaccination humoral response similar to their matched controls. We prospectively measured the titers of neutralizing antibodies (NAbs) against SARS-CoV-2 after vaccination with the Pfizer-BioNTech BNT162b2 mRNA vaccine and analyzed for factors that were related to seroconversion.

This report is part of larger prospective study (NCT04743388) assessing the kinetics of anti-SARS-CoV-2 antibodies development after COVID-19 vaccination. The major inclusion criteria for this

analysis include: (i) a prior diagnosis of AL or ATTR amyloidosis and, (ii) eligibility for vaccination. As a control group, we used volunteers matched for age, gender (1:2), who had (i) no autoimmune or active malignant disease; (ii) no Human Immunodeficiency Virus (HIV) or active hepatitis B, C infection. Serum was separated within 4 h from blood collection and stored at  $-80^{\circ}\text{C}$  until the day of measurement. Collected samples refer to day 1 (D1; first BNT162b2 dose), day 22 (D22; second dose), and day 50 (D50; i.e., 4 weeks after the second dose of the vaccine). NAbs against SARS-CoV-2 were measured using an FDA approved surrogate assay (ELISA, cPass™ SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ). We used the 30% inhibition cut-off for this surrogate NAbs test as previously suggested<sup>10</sup>; a titer of at least 50% is considered a clinically relevant threshold for viral inhibition.<sup>11</sup> The study was approved by the respective Ethical Committees in accordance with the Declaration of Helsinki and all patients and controls have provided written informed consent prior to enrollment. The primary end point of the study was the NAbs titer on D50. Details of the analysis are provided in the online supplement.

The final analysis included 126 fully monitored patients who were included in the final analysis (68 males/58 females, median age: 66, and range 35–86). The control group included 252 (ratio 1:2) fully matched controls (for age, gender) (136 male/116 females; median age: 66, and range 35–86 years). The median body mass index (BMI) of patients with AL amyloidosis was  $25.4\text{ kg/m}^2$  (range 17.9–42.4) and of controls was  $26.2\text{ kg/m}^2$  (range 17.4–42.7) ( $p = .704$ ).

At the time of vaccination, 66 (52%) patients with AL amyloidosis were on active therapy, 29 (24%) were on daratumumab-based therapy, 8 had completed therapy but <3 months from the first dose of the vaccine and 52 (43%) had discontinued therapy >3 months from the date of the first vaccine shot, 33 (27%) had prior exposure to daratumumab (at least 3 months had passed since the last dose), and 92 (75%) were in hematologic remission (hematologic Complete response [CR] or hematologic very good partial response [VGPR]). Among those

not on therapy, median time since last dose was 26 months (range 3–118). More patients' characteristics are shown in Table S1.

Prior to the first dose (D1), the NAb titers were similar between patients and controls (median 14.9% [IQR 7.8%–23.1%] vs. 14% [IQR 6.8%–22.9%],  $p = .439$ ). Eight (6.5%) patients with AL amyloidosis patients had baseline NAb titers  $\geq 30\%$  (positivity cutoff), of which five reported a history of prior COVID-19 infection. Among controls, 24 (9.9%) had NAb titers of  $\geq 30\%$  (Figure 1A).

On D22 after the first dose of the BNT162b2 vaccine, there was a significant increase of NAb titers both in controls and AL patients (both  $p < .001$ ); however, the median NAb titer was 23.6% (IQR 12.4%–37.7%) in patients with AL amyloidosis versus 47.5% (IQR 32.1%–62.7%) in the control group ( $p < .001$ ). Thus, 18% of AL patients versus 44.7% of controls ( $p < .001$ ) developed NAb titers  $\geq 50\%$ ; this level of Nabs is associated with clinically relevant viral inhibition<sup>11</sup> (Figure 1A).

On D50 after the initial vaccine shot (4 weeks after the second shot), there was further increase in NAb titers both in controls and AL patients (for both  $p < .001$ ) and median NAb titer for AL patients was 83.1% (IQR 41.5%–94.9%) versus 95.6% (IQR 91.7%–97.2%) in controls ( $p < .001$ ). Thus, after completion of the two doses, 71% of patients with AL amyloidosis versus 98% of matched controls ( $p < .001$ ) developed NAb titers  $\geq 50\%$  (Figure 1A).

In univariate analysis, factors associated with NAb titers on D50 included age ( $p < .001$ ), lymphocyte counts ( $p < .001$ ), serum albumin ( $p < .001$ ) and amount of proteinuria at the time of vaccination ( $p = .047$ ), renal involvement ( $p = .047$ ), use of steroids ( $p < .001$ ), active treatment ( $p < .001$ ), treatment-free interval ( $p = .001$ ) and remission status (CR/VGPR vs. PR/NR) ( $p = .018$ ). There was no significant association of D50 NAb titers with gender ( $p = .092$ ), BMI ( $p = .198$ ), serum IgG (0.099), IgA ( $p = .789$ ), or IgM levels ( $p = .687$ ) or low (i.e., below lower limit of normal) of at least one of the noninvolved immunoglobulin ( $p = .179$ ) at the time of vaccination, as well as of liver ( $p = .521$ ) or heart involvement by amyloidosis ( $p = .141$ ).

Patients on active therapy had lower NAb titers at D50 (median 51.5% [IQR 25.3%–84.1%] vs. 91.6% [IQR 74.5%–96.5%]) compared to those not on active treatment ( $p < .001$ ). Specifically, 51% of patients on anti-clonal therapy had a D50 NAb titer  $\geq 50\%$  versus 87% of those who were not on therapy. There was no difference in the baseline NAb titers among those on or off active therapy, while on D22 (i.e., after 1st dose) the NAb titer was higher among those on therapy but statistical difference was marginal (median 30% vs. 19.6%,  $p = .052$ ). Thus, after the second dose, the response among those not on therapy was substantially more robust than in patients receiving anti-clonal therapy (Figure 1B). Notably, on D22, NAb titers among AL patients not on active therapy were still significantly lower as compared to non-AL controls (median 27.9 vs. 46.7%,  $p < .001$ ) as well as on D50 (median 91.6% vs. 95.6%,  $p < .001$ ). Using receiver operating characteristic (ROC) analysis, we found that at least 3 months since the last dose of therapy were associated with significantly higher probability of  $\geq 50\%$  NAb titers on D50 (sensitivity: 62%, specificity: 80%, AUC: 0.690,  $p = .001$ ).

Among patients on treatment, there was no significant difference between those on bortezomib-based therapy (VCD) versus those on daratumumab-alone therapy, those on daratumumab with VCD or those on IMiDs, or those with current or prior use of cyclophosphamide. Active therapy containing daratumumab did not affect NAb titers among patients on active therapy (median NAb titer was 52.1% vs. 46.4% for those not receiving treatment with daratumumab,  $p = .486$ ). Similarly, among patients not on active treatment, prior exposure to daratumumab did not affect D50 NAb titers (92.1% vs. 91.2%,  $p = .966$ ) (Figure 1C). Six (5%) patients had a history of prior autologous stem cell transplantation (ASCT) with a median time since transplant of 61 months, (range 6–184); median NAb titer at D50 was 89% for this group of patients with two patients having NAb titers below 50%.

Generalized linear models after normalization of NAb titers, were used for evaluation of multiple factors associated with D50 NAb titers (Table S3). Specifically, at least 3 months since the last dose of anti-clonal therapy ( $p < .001$ ), lymphocyte counts ( $p = .001$ ) and serum albumin levels at the time of vaccination ( $p = .020$ ) were independent predictors of NAb titers on D50.

Focusing on significant (i.e., protective) seroconversion (defined as NAb titer  $\geq 50\%$  at D50), we performed a multiple logistic regression analysis. In this analysis,  $>3$  months of treatment-free interval (OR: 7.75,  $p < .001$ ), was the strongest predictive factor associated with activation of humoral immune responses (Table S2).

Among the patients in the study, one was infected and developed very mild symptoms after the first and before the second dose and two patients were infected but remained completely asymptomatic more than 2 weeks after the second dose (in both testing was performed because of close home contact with an infected individual).

We also compared NAb titers of patients with ATTR<sup>wt</sup> ( $N = 22$ ) to age and gender matched controls ( $N = 44$ , 1:2 matching, median age 84, range 72–92 in both) (Table S4) that were vaccinated with BNT162b2; 18 (82%) of the patients were receiving tafamidis (61 mg dose). The median baseline NAb titers were similar (23% for patients with ATTR<sup>wt</sup> vs. 16% for controls,  $p = .717$ ) as well as on D22 (40.5% for ATTR<sup>wt</sup> vs. 41.2% for controls,  $p = .596$ ) and on D50 (92.2% vs. 94.2%,  $p = .546$ ) (Figure S1).

The data presented in this report indicate that patients with AL amyloidosis have an attenuated humoral response to vaccination with BNT162b2, as compared to matched controls. Our analysis indicates that the most important factor that negatively affects the development of NAb titers after vaccination for COVID-19 is the administration of active anti-clonal therapy. This data point to the major immunosuppressive role of anti-plasma cell therapy but also to the immunosuppressive effect of the underlying plasma cell clone, even though the impact may be low. Thus, patients with AL amyloidosis do not differ significantly in their response to vaccination than patients with myeloma (data published from our group<sup>5,6</sup> and others<sup>7,8</sup>). Specifically, we recently reported that antibody response after vaccination with BNT162b2 in patients with myeloma depends on the type of anti-myeloma treatment.<sup>6</sup> In the current study, in patients with AL

amyloidosis, we observed that the use of daratumumab as part of the treatment regimen did not significantly affect antibody response, among those on active therapy, while prior exposure to daratumumab, also did not have any additive immunosuppressive effect. Data from our group in patients with myeloma indicated that daratumumab-based therapy was associated with lower NAb titers<sup>6</sup>; however, myeloma patients were more heavily pretreated than patients with AL amyloidosis and with more extensive and aggressive clones. In addition, weekly bortezomib with cyclophosphamide (the most widely used regimen in AL amyloidosis) is also associated with significant immunosuppression. Time from the last dose of therapy was a significant factor to predict an adequate antibody response; however, some patients may require more time to restore a fully functional immune system. We observed that a duration of at least 3 months after last dose of anti-clonal therapy before vaccination may affect humoral immune response. In support, in an exploratory analysis, not all patients had recovered lymphocyte counts at the time of vaccination (10% of those not in therapy had lymphocyte counts <1000/ $\mu$ L). Although it is recommended that a treatment-free period should precede and follow vaccination, this may not be feasible; in fact, although vaccination is an urgent need for those most vulnerable subjects, 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 NAb titers. We also evaluated a small number of elderly patients with non-AL amyloidosis and no clonal disease (i.e., patients with ATTR<sup>wt</sup> amyloidosis) and observed that they developed an antibody response that was similar to their age/gender-matched controls.

These results clearly support the need for further evaluation of possible booster doses in patients that fail to develop adequate antibody responses. Across these lines of possible interventions, recent data<sup>12</sup> from a small randomized study support that among transplant recipients receiving immunosuppression a third dose of the mRNA-1273 vaccine (Moderna) triggered substantially higher immunogenicity than placebo. Since there are similarities in the level of immunosuppression caused by anti-clonal therapies for AL amyloidosis (as well as for myeloma and lymphomas), a similar strategy is probably a likely indication, but has not yet been approved by the authorities. Nonetheless, our data provide evidence that there is an urgent need to adopt strategies that can enhance a clinically meaningful protective seroconversion in patients with AL amyloidosis (either on therapy or after therapy). Given the ongoing spread of the SARS-CoV-2 B.1.617.2 (or delta) variant with increased infectivity, this need becomes urgent. Recently, a booster dose has been recommended for immunocompromised patients in many countries, including those who had been vaccinated with BNT162b2. Our data indicate that such a strategy could indeed be beneficial for many patients who failed to achieve seroconversion, or who may have waning antibody levels.

Our study was not designed to assess clinical efficacy of vaccination in patients with AL amyloidosis. Among the 126 vaccinated patients, there were only two cases of asymptomatic infection, despite the increasing infection rates in Greece. For the evaluation of

efficacy, we used the previously reported threshold of at least 50% titer for neutralizing antibodies. However, even lower levels of NAb titers may be protective against severe infection,<sup>13</sup> while new variants of SARS-CoV-2 may be associated with resistance to antibodies requiring higher Nab titers for effective clinical protection. There is evidence that NAb against Wuhan strain, elicited after vaccination with current vaccines display significant activity against other variants of concern, including the delta variant, although neutralizing serum responses may be weaker.<sup>14,15</sup> In a recent paper by Rosati et al.,<sup>16</sup> the authors found that anti-spike antibodies from the vaccine recipients (naïve and convalescent) and SARS-CoV-2 convalescent patients show a strong ability to recognize and neutralize the autologous WA1, as well as the Alpha and Delta Spike variants but that they show greatly impaired recognition of Beta, in agreement with others. Furthermore, they found a strong direct correlation between NAb against WA1 and Delta variant, supporting the notion that individuals with robust NAb against WA1 also strongly neutralize Delta. This data indicates that a titer of NAb >50% may not be as protective against delta variant infection, but the clinically relevant threshold is difficult to define. Finally, in the current study, we did not evaluate the antiviral T and B cell memory responses after vaccination, which may also be affected in patients with AL amyloidosis, and which are also important for protection from the infection. In conclusion, patients with AL amyloidosis have a less robust response to anti-SARS-CoV-2 vaccination as compared to matched controls. Our data point to the critical role of concomitant anti-clonal therapy, which significantly reduced the probability of an adequate antibody response and protective seroconversion. Moreover, our data support the need for additional booster doses, especially for those on active therapy.

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



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#### CONFLICT OF INTEREST

**Efstathios Kastritis:** Janssen: Consultancy, Honoraria, Other: Travel/accommodations/expenses, Research Funding; Pfizer: Consultancy; Genesis Pharma: Consultancy, Honoraria, Other: Travel/accommodations/expenses; Amgen: Consultancy, Honoraria, Research Funding; Takeda: Consultancy, Honoraria, Other: Travel/accommodations/expenses. **Evangelos Terpos:** Bristol-Myers Squibb: Honoraria; Sanofi: Honoraria; Celgene: Honoraria; Genesis: Honoraria, Other: Travel expenses, Research Funding; Takeda: Honoraria, Other: Travel expenses, Research Funding; Amgen: Honoraria, Research Funding; Janssen: Honoraria, Research Funding. **Meletios A. Dimopoulos:** Beigene: Honoraria; Bristol-Myers Squibb: Honoraria; Amgen: Honoraria; Takeda: Honoraria; Celgene: Honoraria; Janssen: Honoraria.

## DATA AVAILABILITY STATEMENT

Raw data are available at reasonable request by direct contact with the corresponding author.

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## SUPPORTING INFORMATION

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## Iatrogenic Kaposi's sarcoma in a myelofibrosis patient treated with ruxolitinib: Case-report, literature review, and French pharmacovigilance data

To the Editor:

Kaposi's sarcoma (KS) is a rare lympho-angioproliferative disorder associated with human herpesvirus 8, also known as KS-associated herpesvirus (KSHV).<sup>1</sup> The epidemiological classification describes five presentations of KS, namely: AIDS-associated KS, classic KS in older European men, endemic KS in younger men and children in sub-Saharan Africa, nonendemic KS in men who have sex with men (MSM) with no identifiable immunodeficiency and iatrogenic KS.<sup>1</sup>

Apart from well-described iatrogenic KS occurring among organ transplant recipients, an increasing incidence of KS has been observed in patients on long-term immunosuppression for other diseases.<sup>1,2</sup>