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European Journal of Internal Medicine 99 (2022) 104–105

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

# T-cell response to 3 doses of Sars-Cov2 BNT162b2 Pfizer vaccine in long term rituximab treated patients

ARTICLE INFO

*Keywords*
T-cells
SARS Cov2 vaccine
Rituximab

B-depleting therapies increase the risk of severe COVID-19 [1] and have been shown to induce an impaired immune response to the SARS-COV2 vaccine [2]. There is a lack of data exploring the T-cell response to SARS COV2 vaccine [3,4], especially since it may be preserved in patients treated with rituximab [5].

Here we analyzed the T-cell immune response to SARS Cov2 vaccination measured by interferon-γ release assay (see details in sup file) after three Pfizer BNT162B2 mRNA vaccine doses (see details in sup file) in 28 long term rituximab-treated patients and compared the characteristics of patients according to the good or poor T-cell response to the vaccine.

Patients received rituximab for ANCA-associated vasculitis ($n = 13$), Ig-G4 related disease ($n = 4$), immune thrombocytopenia ($n = 3$), anti-MAG neuropathy ($n = 3$), dermatomyositis ($n = 1$), systemic sclerosis ($n = 1$), rheumatoid arthritis ($n = 1$), Waldenström macroglobulinemia ($n = 1$) and chronic polyradiculoneuropathy ($n = 1$). Median disease duration at inclusion was 6 years [2.0–10.75] without difference between vaccine responders and non-responders. Patients had received a median of 6 infusions [IQR: 4.0–13.0] of rituximab at inclusion with a median duration between the last infusion and inclusion less than 6 months (125.5 days [86.25–182.0], without any difference between the 2 groups ($P = 0.9454$). Sixteen patients (57%) had a preserved T-cell response after the third dose of vaccine. These patients were younger (median 56.5 years IQR [33.75–63.5] vs. 71.0 [66.5–76.25]; $P = 0.0003$). There was no difference depending on the underlying disease, the number of infusions of rituximab, previous therapies or low dose concomitant steroid therapy ($n = 8$, median daily dose 5 mg [5.0–8.75]).

Total lymphocytes count ($x10^9$/L) was higher in responder's patients (1.53 [1.170–1.890] vs. 1.010 [0.6525–1.170]; $P = 0.0003$). Number of patients with B-cell reconstitution was higher in responders patients (7 vs 0; $P = 0.003$). The percentages of CD3+ lymphocytes, CD3+CD4+ lymphocytes, CD3+CD8+ lymphocytes and NK cells were similar between groups ($P = 0.4345$, $P = 0.7692$, $P = 0.6548$ and $P = 0.0550$, respectively). A total of 10 patients had serological response toward SARS Cov2 vaccine, as defined by anti-SARS Cov2 Ig-G titers >50 UA/ml. This titer tends to be higher in patients with a T-cell response (11.10 [2.125–1893] vs 1.30[0.25–107.7]; $P = 0.0833$). All data are reported in Table 1.

Multivariate analysis (age≥65 yes/no, T lymphocytes<1 × $10^9$/L yes/no, B cell reconstitution yes/no) using backward binary logistic regression showed that age ≥65 years (odds ratio[OR]=0.034 [95% CI=0.003–0.428]; $P = 0.009$) and T lymphocytes<1 × $10^9$/L (OR=0.047 [0.003–0.887]; $P = 0.047$) were significantly associated with a poor T-cell response.

Our data show that most rituximab-treated patients have a poor humoral response to SARS-Cov2 after complete vaccination with 3 doses of Sars-Cov2 BNT162b2 Pfizer vaccine and surprisingly, some have an additional T-cell immune response defect, suggesting that the risk of a severe form is further increased in these patients.

Among factors specifically associated with poorer T-cell immune response, we identified the number of T lymphocytes and age ≥65 at the time of vaccination. By contrast and as previously reported [2], there was no correlation between disease duration, previous drug exposure or time since last rituximab infusion and T-cell response.

It is of concern that some rituximab-treated patients do not develop a humoral or T cell response after vaccination and should therefore be prioritized to receive prophylactic cocktails of neutralizing antibodies, especially during epidemic periods [6].

In case a study of the anti-SARS Cov2 cellular immune response is not possible, consideration of age and circulating T cell count may predict a poor T-cell immune response after SARS Cov2 vaccination.

To conclude, T-cell response to the BNT162B2 mRNA vaccine in rituximab-treated patients is primarily determined by age and T-cell count.

## Disclosure

The authors declare non competing finical interest related to this study.

## Patient consent for publication

Not required

https://doi.org/10.1016/j.ejim.2022.01.030
Received 10 January 2022; Received in revised form 16 January 2022; Accepted 18 January 2022
Available online 24 January 2022

**Table 1**
Patient characteristics depending on T-cell response to SARS-COV2 vaccine in Rituximab-treated patients.

| | All($n$ = 28) | Post vaccinal T-cell response($n$ = 16) | No post-vaccinal T-cell response ($n$ = 12) | P value |
|---|---|---|---|---|
| Age (year old), median [IQR] | 63.0 [55.0–71.0] | 56.5[33.75–63.5] | 71.0 [66.5–76.25] | **0.0003** |
| Sex ratio (M/F) | 17/11 | 8/8 | 9/3 | 0.2530 |
| Underlying disease | | | | |
| ANCA associated vasculitis | 13 | 7 | 6 | >0.9999 |
| Ig-G4 related disease | 4 | 1 | 3 | 0.2850 |
| Immune thrombocytopenia | 3 | 2 | 1 | >0.9999 |
| Anti-MAG neuropathy | 3 | 2 | 1 | >0.9999 |
| Dermatomyositis | 1 | 1 | 0 | >0.9999 |
| Systemic sclerosis | 1 | 1 | 0 | >0.9999 |
| Rheumatoid arthritis | 1 | 1 | 0 | >0.9999 |
| Waldenstrom macroglobulinemia | 1 | 0 | 1 | 0.4500 |
| Chronic polyradiculoneuropathy | 1 | 1 | 0 | >0.9999 |
| Median Disease duration (years) | 6.0 [2.0–10.75] | 8.5[2.250–10.75] | 4.5[2.0–11.50] | 0.4684 |
| Concomitant steroids therapy, n | 8 | 3 | 5 | 0.2309 |
| Prior therapies before rituximab, n | | | | |
| TNF-alpha blockers | 3 | 2 | 1 | >0.9999 |
| Cyclophosphamide | 9 | 4 | 5 | 0.4319 |
| Methotrexate | 6 | 5 | 1 | 0.1965 |
| Mycophenolate mofetil | 4 | 3 | 1 | 0.6132 |
| Azathioprine | 4 | 3 | 1 | 0.6132 |
| tocilizumab | 1 | 1 | 0 | >0.9999 |
| anakinra | 1 | 1 | 0 | >0.9999 |
| abatacept | 1 | 1 | 0 | >0.9999 |
| Numbers of rituximab pulses, median [IQR] | 6 [4.0–13.0] | 6.5[4.0–13.25] | 6 [4.0–13] | 0.7040 |
| Duration between inclusion and last rituximab infusion (days) | 125.5[86.25–182.0] | 116.5[73.75–189.8] | 125.5[102.0–166.8] | 0.9454 |
| Lymphocyte count | 1.190 [0.9875–1.570] | 1.530 [1.170–1.890] | 1.010 [0.6525–1.170] | **0.0003** |
| % of CD19 | 0.0 [0.0–1.0] | 1.000 [0.00–4.00] | 0.000[0.00–0.00] | **0.0037** |
| % of CD3+ lymphocytes | 79.50 [72.50–84.50] | 82.0[74.0–87.0] | 79.0[69.0–82.0] | 0.4345 |
| % of CD3+ CD4+ lymphocytes | 58.0 [41.25–64.25] | 61.0 [36.0–65.0] | 58.0 [46.0–61.0] | 0.7692 |
| % of CD3+ CD8+ lymphocytes | 19.0 [11.75–31.25] | 20.0 [11.0–34.0] | 17.0 [12.0–23.0] | 0.6548 |
| % of CD16+CD56+/CD3-cells | 18.50[12.0–26.75] | 13.00[11.0–23.0] | 20.0[19.0–31.0] | 0.0550 |
| Ig-G anti SARS-Cov2 titer | 4.60[1.0–159.3.8] | 11.10[2.125–1893] | 1.30[0.25–107.7] | 0.0833 |
| B-cell serological response, n (%)* | 10 (35) | 7(43) | 3(25) | 0.4343 |

* Seropositivity was defined by SARS-COV-2 spike antibodies >50 UA/ml.

## CRediT authorship contribution statement

**Jade Heitz:** Conceptualization, Investigation, Data curation, Writing – original draft. **Jerome Razanamahery:** Investigation, Formal analysis, Writing – original draft. **Sylvain Audia:** . **Jean-Baptiste Bour:** . **Julien Guy:** . **Sabine Berthier:** . **Vanessa Leguy:** . **Thibault Ghesquiere:** . **Barbara Nicolas:** . **Maxime Samson:** . **Bernard Bonnotte:** .

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.01.030.

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