SARS-CoV-2 T-cell responses after one or two COVID-19 vaccine boosters in allogeneic transplant recipients

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Introduction:

A full exploration of immune responses is deserved after anti-SARS-CoV-2 vaccination and boosters, especially in the context of allogeneic hematopoietic stem-cell transplantation (Allo-HSCT). Although several reports indicate successful humoral responses in such patients, the literature is scarce on cellular specific immunity. We recently reported a strong response of specific anti-SARS-CoV-2- CD4+ T-cells, with a IFNγ–/TNFα+ cytokine profile, in 89% of humoral responders and 40% of non-humoral responders *(Clémenceau B, et al. Vaccines (Basel). 2022 Mar 14;10(3):448).*

In this study, we have evaluated humoral and T-cell responses **after one (V3 group n=40**) or **two (V4 group n=12) BNT162b2 mRNA vaccine boosters in 52 Allo-HSCT patients** and in 12 healthy donors. For V3 group, the median time between allo-HCT and V3 vaccination was 869 days (167-5160). For V4 group, the median time between allo-HCT and V3 vaccination was 267 days (143-1090) and 459 days (239-1306) between allo-HCT and V4 vaccination.

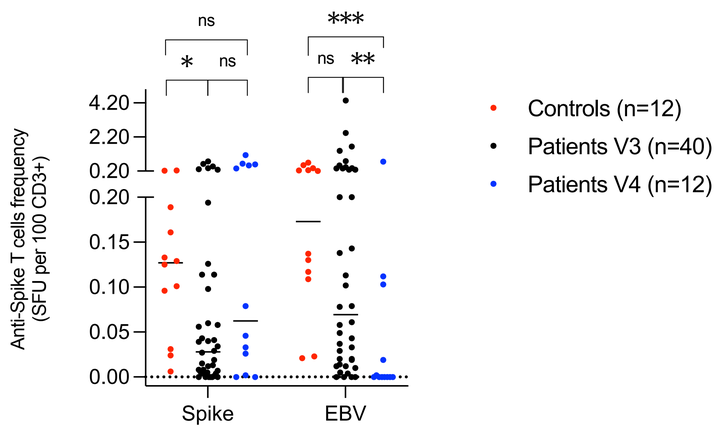
Methods:

Blood samples were collected between January 18th and March 3rd 2022 during the Omicron wave in France. Anti-spike antibodies were tested using anti-SARS-CoV-2 immunoassay Elecsys® (Roche, Rotkreuz, Switzerland). Anti-SARS-CoV-2 Spike and anti-EBV (as positive control) specific CD3+ T-cell responses were evaluated using Human INFγ ELIspot (Mabtech, Nacka Strand, Sweden) and intracellular cytokine staining after peptide stimulation (PepTivator Prot_S Complete, Miltenyi Biotec, Bergisch Gladbach, Germany).

Results :

All controls (100%) and **81% of the whole patient cohort have developed a protective anti-S antibody level (>250 BAU/mL) after the boost vaccinations**. The rate of subject reaching the highest antibody concentration (>2500 BAU/mL) was significantly higher in controls than the whole patient cohort (100% vs 52%, p=0.005).

A



After the booster vaccination, 85% of patients and 100% of controls developed a specific-T cell response. The median frequency of anti-Spike T-cells was significantly lower for patients with one vaccine boosters (V3, median = 0.028%) compared to controls (0.127%) but not significantly different between V3 patients and V4 patients (median = 0.063%).

Importantly, considering the patients with no antibody response (n=5) or not reaching a protective antibody level after boosts (n=5), 8/10 (80%) had a measurable T-cell response.

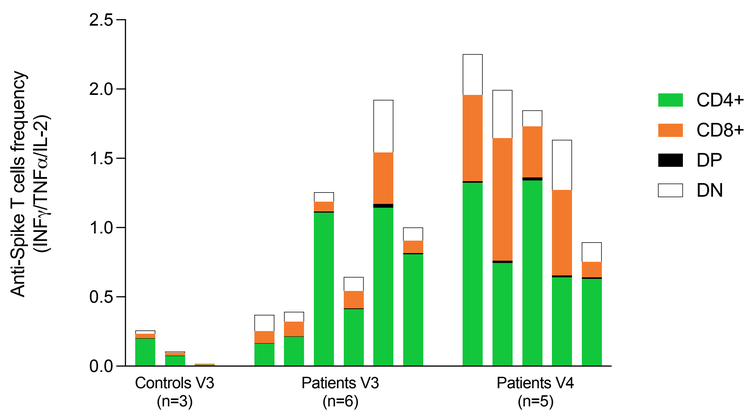
B

Table 1. Factors predicting T-cell response: Univariate analysis

Factors	No responders n=8	Responders N=44	P value
Number of vaccines received: 3/4	6/2	34/10	1
Anti-spike antibody rate: <=250/<250 BAU/ml	2/6	8/36	1
Gender: male/female	8/0	25/19	0.053
Median age: years (range)	57 (49-71)	53 (20-74)	0.84
Disease: lymphoid/myeloid	3/5	13/31	0.97
Donor type: geno/MUD/haplo/mis-m	1/5/2/0	14/17/11/2	0.54
Conditioning: MAC/RIC/Sequential	2/6/0	6/35/3	0.56
GVHD prophylaxis: ATG/Csa+MMF+PTCY/PTCY alone	5/2/1	23/11/10	0.79
Previous GVHD: no/yes	3/5	17/27	1
On-going treatment: no/yes	7/1	34/10	0.85
Median delay V3/V4-analyses: days (range)	94 (12-295)	136 (16-298)	0.46
Median delay graft-analyses: days (range)	703 (356-4047)	755 (189-5293)	0.70
Lymphocytes: Giga/L (range)	2.66 (0.75-3.96)	1.37 (0.12-7.14)	0.053
CD3+ T cells: Giga/L (range)	1.58 (0.23-2.25)	0.68 (0.09-3.90)	0.09
CD4+ T cells: Giga/L (range)	0.38 (0.07-1.04)	0.34 (0.04-2.05)	0.77
CD8+ T cells: Giga/L (range)	**0.84 (0.13-1.56)**	**0.34 (0-1.94)**	**0.03**
B cells: Giga/L (range)	0.28 (0-0.65)	0.27 (0-1.61)	0.75
NK cells: Giga/L (range)	**0.35 (0.15-0.51)**	**0.18 (0.04-1.03)**	**0.02**
Gamma globulins: g/l (range)	7.7 (3.4-17.3)	6.75 (1.1-13.9)	0.53

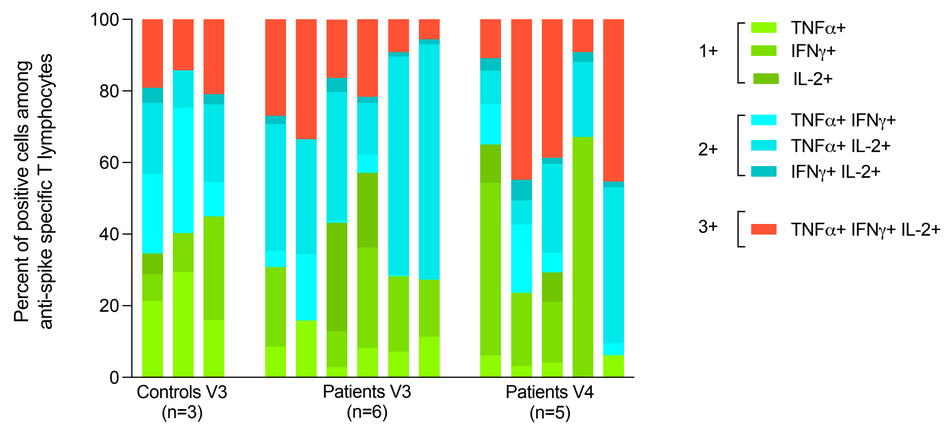
The only factors predicting T-cell response were CD8+ and NK cells counts at time of analyses. For CD8+, this data was also recently reported by Meyer T et al (Vaccines. 2022 oct, 10, 1782).

C



For 14 individuals with the highest frequencies of anti-Spike CD3+ T cells (> 0.180 SFU/100 CD3+ T-cells), the Th1 cytokine of CD3+ T-cell subsets were assessed by INFγ, TNFα and IL-2 intracellular staining and **a predominance of anti-spike CD4+ T-cell response was observed.**

D



Seven cytokine secretion profiles were analysed on specific anti-spike CD3+ T-cells and interestingly, **polyfunctionality T-cells (3+ : INFγ, TNFα and IL-2 positives) were observed in both controls (n=3), and patients (n=11).**

At time of last follow-up (June 1st 2022), two V3 patients have presented a non-severe COVID 19 infections (one with a negative serology and 0.039 SFU/100 CD3+ T-cells and the second with a serology >2500 BAU/mL and 0.040 SFU/100 CD3+ T-cells). One V3 patient with negative serology and 0.367 SFU/100 CD3+ T-cells at time of analysis have died of COVID-19 infection.

Conclusion: In this cohort after one or two booster vaccination, 81% of patient achieved a protective humoral response while 85% achieved a T-cell response. The median frequency of anti-Spike T-cells among CD3+ T-cells was lower in the cohort patients (0.034%) than in controls (0.127%) but not statistically significantly different. Interestingly, polyfunctionality T-cells were observed in both controls and patients. Higher CD8+ and NK lymphocytes counts negatively influenced anti-Spike T-cells response. COVID-19 infections were solely observed in individuals having received only one booster. These results indicate that four vaccine injections help to achieve a satisfactory level of both humoral and cellular immune protection in Allo-HSCT patients.

Clémenceau B, Le Bourgeois A, Guillaume T, Coste-Burel M, Peterlin P, Garnier A, Jullien M, Ollier J, Grain A, Béné MC, Chevallier P. Strong SARS-CoV-2 T-Cell Responses after One or Two COVID-19 Vaccine Boosters in Allogeneic Hematopoietic Stem Cell Recipients. Cells. 2022 Sep 27;11(19):3010.