INDUCTION OF NEUTRALIZING ANTIBODIES IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) PATIENTS AFTER SARS-COV-2 MRNA VACCINATION: A MONOCENTRIC EXPERIENCE

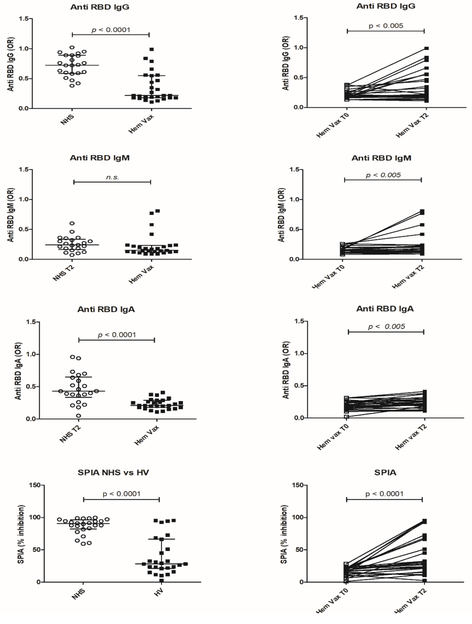
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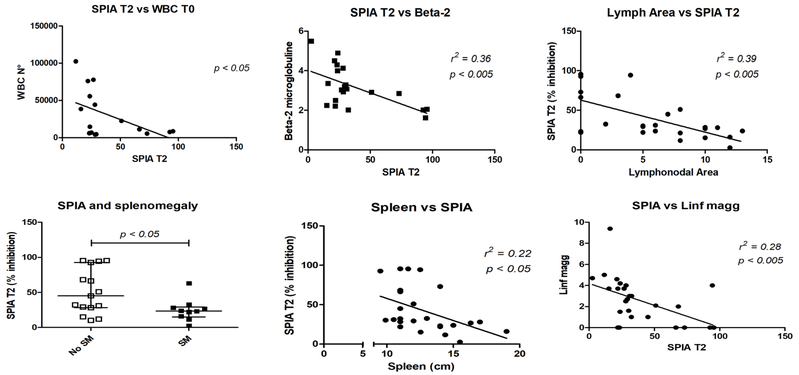
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Introduction

In chronic lymphocytic (CLL) patients, either the immune system highly dysregulated by the disease or the immune deficiency due to anti-leukemic treatment concur in inducing impairment of immune responses and contribute to increase frequency and severity of infections and to reduce response to vaccines[1]. Several studies evaluated the response of CLL patients to mRNA SARS-CoV2 vaccines, measuring serum anti-spike antibodies after one[2], two[2,3], or three[4] doses. Marked impairment of the immune response was observed, with a response rate of 40-75%. In this report, we analyzed anti-RBD and neutralizing antibodies in CLL patients comparing them with the immune responses observed in healthy individuals after two doses of the mRNA vaccine.

Parameter	Patients with CLL (N = 27)
Age, median, y	70,6
age </= 65 y, N (%)	4 (14.8%)
Male sex, N (%)	18 (66.7%)
Disease/treatment status, N (%)	
treatment-naive	10 (37%)
on-therapy	13 (48.1%)
off-therapy in remission	4 (14.9%)
Binet stage (treatment-naive pt) N (%)	
A	4 (40%)
B	6 (60%)
C	0 (0%)
IGHV mutational status, N (%)	
mutated	2 (15.4%)
unmutated	11 (84.6%)
FISH, N (%)	
normal	9 (34.6%)
del(13q)	6 (23.1%)
trisomy 12	6 (23.1%)
del(11q)	4 (15.4%)
del(17p)	1 (3.8%)
TP53 status	
wild type	14 (93.3%)
mutated	1 (6.7%)
Beta2-microglobulin, N (%)	
</= 3.5 mg/L	15 (75%)
> 3.5 mg/L	5 (25%)
Protocols of currently treated, N (%)	
BTKis	6 (46.2%)
Venetoclax +- anti-CD20 antibody	4 (30.8%)
others	3 (23%)
Laboratory parameters, median	
ALC (10^9/L)	19,95
Beta2-microglobulin, mg/L	3,18
IgG, mg/dL	767,5
LDH, U/L	212,67
Hb, g/dL	13,72



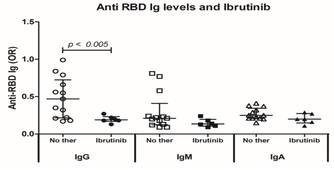


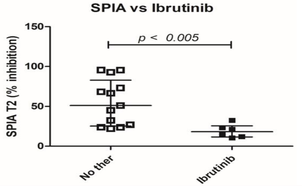
Materials & Methods

Twenty-seven CLL patients regularly followed at the Hematology Unit of Pisa University Hospital and vaccinated against SARS CoV-2 were recruited into the study. At the time of enrolment, the following clinical data were collected for each patient: age, gender, stage of disease, treatment status, laboratory parameters, and presence of hypogammaglobulinemia. Analyses of genomic aberrations by fluorescent in situ hybridization (FISH) and mutational status of the immunoglobulin heavy chain variable (IGHV) gene have been also included.
Twenty-one health care workers (normal healthy subjects – NHS), vaccinated with mRNA BNT126b2, served as the control group (mean age ± SD = 46.8 ± 12.9; M/F = 5/16). Whole blood was collected before the first dose (T0) and from 11 to 41 days after the second dose (T2), with a median time of 23 days.
No patient nor any control previously contracted SARS-CoV-2 infection before recruitment for the study. The median age was 70.6 years, with a prevalence of males (66.7%). Binet disease stage was A in 40% and B in 60% of cases. Predominant IgHV mutational status was unmutated (84.6%). Only one patient resulted in TP53 mutated. About treatment status, 37% of patients were treatment naïve, 48.1% were on therapy and 14.9% were off therapy after achieving clinical remission; 46.2% were on ibrutinib, and 30.8% were on venetoclax (monotherapy/plus rituximab); one patient was on idelalisib.

Discussion

- Anti-RBD IgG were produced in 11/27 (40.5%) of patients while IgM and IgA were induced in 4/27 (14.8%) and 5/27 (18.5%), respectively. Data obtained in vaccinated health care workers are shown in the figure as control.
- NAbs were detectable in 12/27 (44.5%) of the patients, compared with 100% of healthy controls, and their level was lower than that observed in controls.
- The two-doses vaccination procedure induced an overall immune response in 12 out of tested subjects (44.4%).
- Stratifying patients according to the presence of neutralizing antibodies after the vaccination we found a larger prevalence of NAbs positives compared to NAbs negatives in treatment-naïve patients (60% vs 40%). Patients in clinical remission after therapy had a comparable result (75% versus 25%), however, patients on treatment had a much lower percentage of NAbs positives (23.1% vs 76,9%).
- Among subjects under therapy, only one out of 7 patients (14.3%) receiving ibrutinib developed an immune response; in addition, in these positive cases levels of anti-RBD IgG and NAbs were lower than those measured in controls.
- The titer of NAbs antibodies was inversely correlated with baseline WBC number, beta-2 microglobulin levels, major lymph node dimension, spleen dimension, and with affected lymph nodes number.





References

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