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Assessment of COVID-19 Vaccine Immunogenicity Over One Year in Patients Receiving Immunomodulators/Immunosuppressants or Polychemotherapy

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Abstract **Original Research Article**

Objective: The aim of the study is to evaluate the immunogenicity of the covid-19 vaccine in patients receiving immunomodulators/immunosuppressants or polychemotherapies based on the treatment of the underlying pathology in an internal medicine and onco-hematology department over a period of one year. ***Materials and methods:*** Our study was prospective. We included 61 patients. They were all undergoing immunosuppressive therapy or polychemotherapy and had been vaccinated against covid. We performed a series of 9 serological tests before vaccination and 21 days after vaccination, at d+49 after a 1st boost, at 3 months, 6 months, 9 months and 12 months. Only 21% of our patients received a 2nd boost. We divided our population into 4 groups according to the treatments received. ***Results***: The results show a mean age of 50 years +/- 14.85. The sex ratio F/M was +/- 1.10. To better characterize vaccine responders, we compared them with non-responders based on several parameters: age, sex, comorbidities, whether or not the third booster dose had been received, biological work-up, specifically anemia, neutropenia, lymphopenia, hypogammaglobulinemia, and treatments divided into four groups: A lack of vaccine response was not significantly correlated with the use of rituximab at S4, i.e., 3 months (p=0.01), at S6, i.e., 9 months (p=0.034), and at S7, i.e., 12 months (p=0.009). Lack of vaccine response at 12 months was significantly correlated with patients receiving polychemotherapy (p=0.02) or immunosuppressive therapy (p=0.043). Multivariate analysis showed an association between lack of vaccine response at S3 in patients receiving rituximab (p=0.024) and corticosteroid therapy (p=0.02) and in leukopenic patients (p=0.04). At 12 months, i.e., S7, a strong association was found between lack of vaccine response in patients on immunosuppressants (p=0.002) and multidrug therapy (p=0.001).

Keywords: Covid-19 vaccin, serology test, immunogenicty, hemopathies and autoimmune disease.

INTRODUCTION

Vaccination is a primary prevention form of care acting before the onset of a disease. It is a cornerstone of preventive therapy for patients with hemopathies or autoimmune diseases [1].

As people with diseases requiring immunosuppressive drugs or multidrug therapy were under-represented in the phase 3 clinical trials of COVID 19 vaccines, several studies were carried out in to assess vaccine efficacy in this population.

To date, it has not been possible to define a threshold antibody level of protection. A positive test could give false reassurance of effective protection. The French health authority considers that the conclusions drawn from post-vaccination serology in immunocompromised patients are currently debatable. Furthermore, the level of neutralizing antibodies (even if directed against the receptor binding domain of the Spike viral protein) cannot be quantified by simple serology. Finally, it's not just the humoral response that matters, as

the cellular immune response also plays a crucial role in the response to Covid-19 vaccines [2].

Our study aims to evaluate the immunogenicity of Covid-19 vaccine in patients receiving immunomodulatory/immunosuppressive or multidrug therapy.

MATERIALS AND METHODS

We conducted a prospective study over two years, from January 2021 to December 2022, in the Department of Internal Medicine and Onco-Hematology, in collaboration with the laboratory of Epidemiology, Clinical Research and Community Health in the University Hospital and Department of Biological Laboratory.

We recruited 61 patients. They were all treated with immunosuppressive drugs or polychemotherapy and vaccinated against covid 19.

We performed a series of 9 serological tests on our patients, before vaccination (S1) and 21 days after vaccination (S2), at d+49 after the 1st vaccination (S3), at 3 months (S4), 6 months (S5), 9 months (S6) and 12 months (S7). All patients received their first booster. Only 21% of the patients received the 2nd booster.

The SARS-COV-2 IgG qualitative and quantitative assay is a chemiluminescent microparticle immunoassay for the qualitative detection and quantitative determination of IgG antibodies specific to SARS-COV-2 in human serum and plasma. IgM detection was not performed on the ARCHITECT I System analyzer in our study.

Our patients had received the various vaccines available, including mRNA, viral vector and live attenuated vaccines (Sinopharm, Astra Zeneca and Pfizer).

1. Study group:

To better study our population, we divided them into 4 large groups based on the treatments they were receiving:

- A first group of patients on immunosuppressive drugs for autoimmune diseases: Cyclophosphamide, mycophenolate mofetil, azathioprine. Immunomodulators such as hydroxychloroquine and colchicine, and anti-metabolic drugs such as methotrexate were included in the same group.
- A second group of patients receiving polychemotherapy for hemopathies such as Thalidomide, Lenalidomide, Polychemotherapy (ABVD, BEACOPP, VDT, CDT, LITAK).
- A 3rd group of patients on corticosteroids alone (more than 10mg/d).
- A fourth group of patients receiving anti-CD20 monoclonal antibody (rituximab) alone or in combination with multidrug therapy (R+/- multidrug therapy).

2. Data collection:

Data were prospectively collected including socio-demographic data, history of COVID 19, current pathology and treatment, and biological data (blood cell count + sedimentation rate + C-reactive protein + serum protein electrophoresis).

3. Follow-up of participants:

Patients were followed up in two ways:

- Regular face-to-face visits were scheduled to assess disease progression and treatment continuity during this study period.
- Serological follow-up throughout the study. Patients were regularly informed of their results.

4. Biological analysis:

Serological tests were performed on fresh samples. Blood samples were collected in a pre-identified dry tube and sent to the laboratory serology unit, where the technician centrifuged the tubes and ran them through the Architect I 1000 and I 2000 automated systems.

We systematically screened for COVID-19 infection using qualitative serology before administering the first dose of vaccine.

The first serological test used for pre-vaccination seroprevalence studies is a qualitative test that detects IgG directed against nucleocapsid protein N (anti-N). A second serological test used in post-vaccination immunogenicity studies is quantitative and detects IgG directed against the SARS-CoV-2 spike protein (anti-S) with antibody levels above 50, following the recommended use of the kit.

5. Statistical analysis

The collected data was coded, recorded and confirmed using Excel software. Statistical analysis was performed using SPSS version 26 software. Descriptive statistics were used, with quantitative variables expressed as means and standard deviations, and qualitative variables expressed as absolute numbers and percentages. Bivariate analysis was performed using the $\chi 2$ test to compare percentages and Student's T-test to compare means. Multivariate analysis was performed using logistic regression to show the absence of vaccine response at the different time points of covid serologies, considering confounding factors. Significant variables were included in the logistic regression model.

6. Ethical considerations:

The purpose of the study was clearly explained to the participants to obtain their consent by signing the informed consent form.

The Ethics Committee of our Faculty of Medicine and Pharmacy, number 09/21, approved the entire protocol and information documents.

RESULTS

N=61. Mean age 50 +/- 14.85 years. A predominance of 68% of the population was between 30 and 60 years of age. The sex ratio F/M was 1.10.

The patient groups, divided according to the treatment received, were followed up for the different pathologies listed below, as described in Table 1.

Table 1: Distribution of the population according to pathologies.

Hemopathies **63.3 % (i.e., n = 38)**		**Auto-immune diseases** **36.7 % (i.e., n= 23)**	
Diffuse large B-cell lymphoma	43.12 %	Connectivitis	17.4%
Multiple myeloma	12 .95 %	Uveitis	9.7%
Hodgkin's disease	10.26%	Vasculitis	4.8%
CLL	7.74%	ITP	3.2%
Tricoleucyte leukemia	2.55%	Other	1.6%

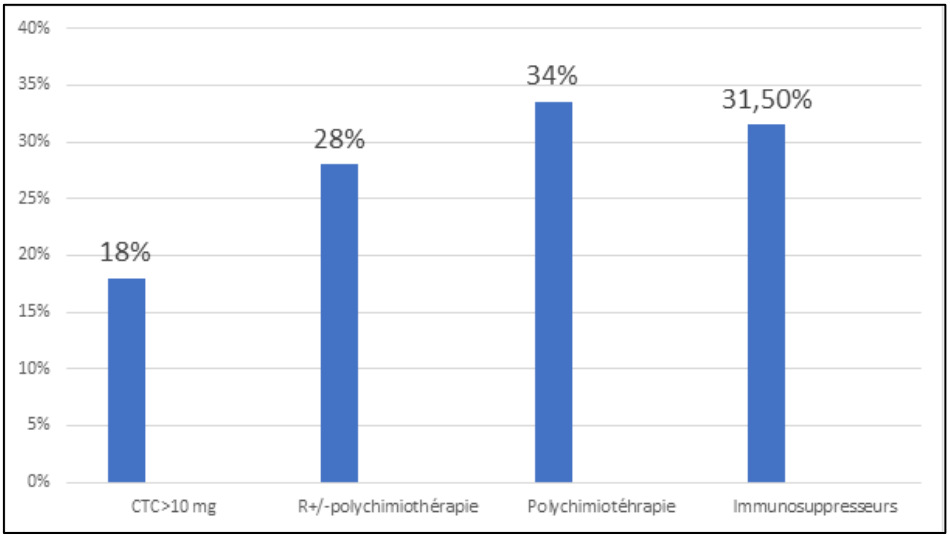

Figure 1: Distribution of patients according to treatments received

Inflammatory tests (CBC, ESR, CRP and EPP) carried out on all our patients showed anemia in 42%, lymphopenia in 24%, and elevated ESR and CRP in 49% and 43% respectively, Table 2.

Table 2: Biological features in our patients.

Biological data	Number of patients (n)	Percentage (%)
Anemia	25	42.6
lymphopenia	15	24.6
Neutropenia	5	9.8
Leukopenia	10	16.4
Hypergammaglobulinemia	23	39.3
Hypogammaglobulinemia	1	1.7
Pic monoclonal	6	9.8
Increased sedimentation rate	30	49
Crp >6	26	43

To better characterize vaccine responders, we compared them with non-responders on several parameters: age, gender, comorbidities, whether they had received a 3rd booster or not, biological work-up, more specifically anemia, neutropenia, lymphopenia, hypogammaglobulinemia, treatments divided into four groups:

S4, i.e., 3 months (p=0.01), S 6, i.e., 9 months (p=0.034) and S7, i.e., 12 months (p=0.009). Lack of vaccine response at 12 months correlated significantly with patients receiving polychemotherapy (p=0.02) or immunosuppressive drugs (p=0.043)

Table 3: Biological and therapeutic characteristics at S2.

Characteristics At S2 (d+21 of the 1st vaccine)	**Vaccine responders (24) 39.34%**	**Non-responders to vaccine (37) 60.65%**	***P Value***
Biological assessment			
Leucopenia	2(%)	8(%)	(0.3)
Neutropenia	1(52,72%)	5 (25.71 %)	(0.4)
Lymphopenia	5(67,27%)	10 (65.71%)	(0.1)
Hypogammaglobulinemia	1 (67,27%)	5 (74.28%)	(0.50)
3rd dose received	2(8.33%)	12(32.43%)	(0.6)
Treatments			
Polychemotherapies (34%)	7(29.16 %)	10(27.02%)	(0.7)
Immunosuppressors (31.50%)	6 (18,18%)	10 (14.28 %)	(0.1)
R+/-polychemotherapy (28%)	4(16.66%)	13(35.15%)	(0.16)
CT > 10 mg (18%)	6 (32,72%)	5 (13.51 %)	(0.18)

Table 4: Biological and therapeutic characteristics at S3.

Features S3	Vaccine responders	Non-responders to the vaccine	*P Value*
Biological assessment:			
Leucopenia	1(%)	9(%)	(0.037)
Neutropenia	2%	4(%)	(1)
Lymphopenia	6(%)	9(%)	(1)
Hypogammaglobulinemia	2%	4%	(0.073)
3rd dose received	5(%)	9(%)	(0.76)
Treatments			
Polychemotherapies (34%)	9(29.16%)	8(27.02%)	(0.26)
Immunosuppressors (31.50%)	8(18,18%)	8(14.28 %)	(0.55)
R +/-polychemotherapies (28%)	1(16.66%)	14(35.15%)	(0.040)
CT> 10 mg (18%)	8 (32,72%)	3(13.51 %)	(0.038)

Table 5: Biological and therapeutic characteristics at S4.

Characteristic S4 (3 months)	Vaccine responders	Non-responders to the vaccine	*P Value*
Biological assessment			
Leucopenia	(%)	10(%)	(0.04)
Neutropenia	1%	5%	(0.38)
Lymphopenia	3 (%)	12(%)	(0.1)
Hypogammaglobulinemia	3%	3%	(0.6)
3rd dose received	5(%)	9(%)	(0.1)
Treatments			
Polychemotherapies (34%)	9(%)	8(%)	(0.2)
Immunosuppressors (31.50%)	9(%)	7(%)	(0.14)
R +/-polychemotherapies (28%)	1(%)	16(%)	(0.01)
CTC> 10 mg (18%)	6 (%)	5(%)	(0.31)

Table 6: Biological and therapeutic characteristics at S6:

Characteristic S6 (9 months)	Vaccine responders	Non-responders to the vaccine	*P Value*
	Biological assessment		
Leucopenia	3(%)	10(%)	(0.01)
Neutropenia	1%	5%	(0.3)
Lymphopenia	2(%)	13 (%)	(0.06)
Hypogammaglobulinemia	3%	3 %	(0.6)
3rd dose received	5(%)	9 (%)	(1)
Treatments			
Polychemotherapies (34%)	8(%)	9(%)	(0.2)
Immunosuppressors (31.50%)	9(%)	7(%)	(0.063)
R +/-polychemotherapies (28%)	2(%)	15(%)	(0.034)
CTC > 10 mg (18%)	5 (%)	6 (%)	(0.4)

Table 7: Biological and therapeutic characteristics at S7.

Characteristic S7 (12 months)	Vaccine responders	Non-responders to vaccine	*P Value*
Biological assessment			
Leucopenia	3(12.5%)	7(18.91%)	(0.3)
Neutropenia	3(12.5%)	3(12.5%)	(1)
Lymphopenia	5(20 .83%)	10(27.02%)	(0.3)
Hypogammaglobulinemia	4(16.66%)	2 (5.40)%	(0.2)
3rd dose received	6(25%)	8(21.62 %)	(1)
Treatments			
Polychemotherapies (34%)	12(50%)	5(13 .51%)	(0.02)
Immunosuppressors (31.50%)	11(45.83%)	5(13.51%)	(0.043)
R +/-polychemotherapies (28%)	3(12.5%)	14(37.83%)	(0.009)
CTC sup 10 mg (18%)	6(25%)	5(13.51%)	(0.7)

Multivariate analysis allowed us to prove an association between lack of vaccine response at S3 for patients on rituximab (p=0.024) and corticosteroid therapy (p=0.02), as well as for leucopenic patients (p=0.04).

At 12 months, i.e., S7, a strong association was found between lack of vaccine response in patients receiving immunosuppressants (p=0.002) and polychemotherapy (p=0.001).

Death was not correlated with vaccine seroconversion.

Study Limitations

Our study does not have a randomized design due to lack of matching between patients and controls.

No data were available on B-lymphocyte levels at the time of vaccination in patients on anti-CD20 therapy, nor on cellular immunity.

Differences between vaccines were not evaluated in this study.

DISCUSSION

Our prospective study is the first nationwide cohort to investigate the impact of vaccine response one year after the first vaccination in an immunocompromised population (on immunomodulators/immunosuppressants or polychemotherapy).

Immunocompromised (IC) patients are those whose immune system is over-activated or suppressed due to an underlying disease or treatment regimen [1]. The most common conditions include malignancies, inherited or acquired immunodeficiencies, autoimmune diseases, transplant patients and other conditions requiring long-term corticosteroid therapy [1]. An estimated 2.7 US adults are affected by IC disease [2]. These patients are at increased risk of severe SARS-CoV-2 infection, longer hospital and intensive care unit stays, and higher mortality compared to the general population [3-7].

The use of GCs is a key factor in the reduction of vaccine immunogenicity compared to other treatments (polychemotherapies, immunosuppressants). In our study, a significant (p=0.02) decrease in response on d+49 after the 1st vaccination was observed. Immunogenicity was enhanced after the 1st and 2nd boosters in the light of later serological results. This suggests that GCs should be carefully prescribed to these vulnerable patients.

Caution should be exercised if IC patients develop leukopenia. Close monitoring is essential to avoid infectious complications in the absence of seroconversion at three months after vaccination, as found in our study.

Our study confirms that the use of rituximab changes the efficacy of the vaccine up to 4 months after vaccination. After 12 months, the patient achieved increased seroconversion rates.

Rituximab treatment completely depletes B lymphocytes within 72 hours. Recovery of B-cell counts usually begins 6-9 months after the end of treatment and reaches normal levels after 9-12 months [5]. Although pre-existing plasma cells and antibody levels are unaffected, B-cell depletion after rituximab reduces the humoral immune response to primary antigens. Furthermore, persistent depletion of memory B lymphocytes reduces antibody production even 6-10 months after treatment [6]. Indeed, this six-month depletion of CD20 is associated with immunoglobulin (IgM) hypogammaglobulinemia and, in some individuals, IgA and IgG, exposing IC patients to serious infections [14-16].

When rituximab is used, the memory B cell pool can be depleted once it reaches a pre-defined level, as seen in rheumatoid arthritis, Devic's neuromyelitis, multiple sclerosis plaques and other diseases, while maintaining clinical remission [3, 9, 11-13].

Antibody responses to SARS-CoV-2 infection are known to target multiple viruses, including different spike protein epitopes, while antibodies targeting the receptor binding domain (RBD) are considered neutralizing. Other antibodies target the NCP nucleocapsid protein or non-structural proteins [7]. Neutralizing antibodies become detectable within 7 to 15 days of illness, increase on days 14 to 22, stabilize and then decrease.

Most patients who recover from SARS-CoV-2 infection develop T and B cell memory. It is noteworthy that although SARS-CoV-2 IgG antibody responses begin to decline 20 days after symptom onset, MSCs increase in number and affinity within 6 months of infection, suggesting that the immune response is persistent despite apparent viral clearance [8]. It is therefore thought that persistent memory B lymphocytes rapidly generate antibody-secreting plasma cells of increased specificity upon reinfection, and thus the decline in serum antibodies over time during the convalescent period may contribute to weakened immunity.

Antibody responses are essential for vaccine efficacy, but memory B cells may be equally important for long-term protection and the ability to respond to new variants.

Finally, patients receiving immunosuppressive therapy or polychemotherapy require frequent long-term

follow-up, i.e., at least one year. This would include proper booster vaccinations to match individual seroconversion levels as part of best overall management.

CONCLUSION

Our study showed that immunocompromised patients were not seroconverted to Covid-19 vaccine at 3months, and long after in patients receiving immunosuppressive or hematological therapy. For this, a regular follow-up, with a personalized analysis of Sars-covid serologies and, if possible, Lymphocyte subpopulation is recommended.

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