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Patients at Risk of Pulmonary Fibrosis Post Covid-19: Pulmonary Sequelae and Humoral Response

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Abstract

Background: The COVID-19 pandemic is one of the major public health problems. The aim of this study is to characterize patients hospitalized for COVID-19 pneumonia at risk of pulmonary fibrosis and to know the amount of protective antibodies and their permanence in these patients.

Methods: Follow-up study of the humoral response in hospitalized patients at risk of pulmonary fibrosis post-COVID-19 who were followed up for one year after hospital discharge.

Results: The study included 72 patients, 52 of whom had pre-existing chronic comorbidities. COVID-19 clinical severity was rated in 6% as mild, 58% as moderate and 36% as severe. After one year follow-up, forty percent had pulmonary sequelae, the most frequent being mild pulmonary fibrosis. All patients presented RBD IgG, 88% IgA after 8-9 months. The amount of RBD IgG was similar at 4-5 and 8-9 months post-COVID-19. There was no difference in RBD IgG level according to COVID-19 severity ($P = .441$, $P = .594$).

Conclusions: The amount of RBD IgG is maintained throughout the convalescent phase and could protect against new reinfections in patients at risk of pulmonary fibrosis Post Covid-19. However, it does not seem to predict the development or not of pulmonary fibrosis.

Introduction

The COVID-19 pandemic continues to spread worldwide and is one of the greatest public health problems in the world. The severity of the COVID-19 picture is probably due to a previous deterioration of the immune system [1] due to the comorbidities, such as those reported Williamson et al., [2]: cardiovascular disease, diabetes, respiratory disease including severe asthma, obesity, history of hematological malignancy, cancer, kidney, liver, neurological and autoimmune conditions. Many patients are symptomatic to some degree after COVID-19 infection, but pulmonary fibrosis is exceptional [3]. Little is known about the long-term pulmonary sequelae after COVID-19 infection. The mechanism of post- COVID-19 lung fibrosis is still unclear but is believed to be multifactorial; direct viral effects, the roles of the renin-angiotensin system, production of proinflamamtory cytokines and reactive oxygen species [4]. In the pulmonary fibrosis, acute damage favors the deposition of hyaline material in the alveolar membranes. In a posterior phase, the lungs show fibrin deposition and infiltration of inflammatory cells and fibroblasts, so that eventually the tissue becomes fibrotic. On the other hand, the evolution of antibody immunity in this type of population is unknown.

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Some authors like Horton et al. [5], reported that symptom severity correlated with the magnitude and trajectory of IgG production. But the risk of reinfection is considerable, due to several reasons: the permanence of these antibodies in the organism after a primary infection [6] and the emerging viral variants. The aims of this study are to characterize patients hospitalized for COVID-19 pneumonia at risk of pulmonary fibrosis and to know the amount of protective antibodies and their permanence in these patients.

Materials and Methods

Descriptive characteristics and follow-up results of the humoral response in patients with a diagnosis of SARS-CoV-2 confirmed by RT-PCR and hospitalized at the Hospital Universitario de Canarias, between March and October 2020, who were followed up after hospital discharge at the Multidisciplinary Interstitial Lung Disease Unit of this Hospital. These patients had to present at least one of the following conditions to be referred to such consultation: persistence of pathological alterations in the chest X-ray and/or having required special ventilatory support devices during their admission (high-flow nasal spectacles, noninvasive ventilation or intubation and mechanical ventilation). This follow-up ended when respiratory clinical normalization was observed and complete or almost complete involution of the radiological alterations initially visualized was confirmed. During follow-up and for the evaluation of possible post COVID-19 pulmonary sequelae function tests and imaging tests (pulmonary ultrasound and high resolution computed axial tomography) were performed at 6 weeks (in all cases), at 3-6 months and one year after hospital discharge (those who had to be followed up due to incomplete recovery in the initial and successive visits). Patient volunteers signed the informed consent and were subsequently scheduled for serum sampling at 4-5 months and 8-9 months after COVID-19 infection. Clinical variables of the patients were also collected by reviewing the medical history: sex and age, comorbidities considered as risk factors for worse prognosis [7], being a smoker or former smoker, degree of severity of COVID-19 disease during the hospitalization according to the WHO guidelines (Clinical Management of COVID-19 Patients-Interim Guidance) [8], hospital admission service, hospital stay, duration of the acute phase of the disease, development of pneumonia, measurement of oxygen saturation and type of ventilatory support required during admission, months of post-discharge follow-up, clinical resolution after one year of follow-up, reinfection with SARS-CoV-2. Different antibodies were analyzed in serum samples; RBD-specific IgG, Nucleocapsid IgG, and Spike 1-RBD IgM antibodies determined by Abbott chemiluminescent microparticle assays (CMIA): SARS-CoV-2 IgG II Quant, SARS-CoV-2 IgG and SARS-CoV-2 IgM using the ARCHITECT i 2000 SR system, following the manufacturer's instructions. IgG RBD measurements were transformed to the WHO international standard BAU/mL [9] in order to obtain an internationally comparable quantification of antiSARS-CoV-2 antibodies. IgA Spike and IgM Nucleocapsid antibodies were determined using EUROIMMUN enzyme-linked immunosorbent assay (ELISA); Anti-SARS-CoV-2 ELISA IgA and Anti-SARS-CoV-2 NCP ELISA IgM (Euroinmmun, Lübeck, Germany) according to the manufacturer´s instructions on the Dynex DS2 ELISA System platform. The characteristics of the sample are presented summarizing the nominal variables with the absolute and relative frequency of their component categories and the numerical scale variables with mean (SD) or median (minimum-maximum) according to their normal or non-normal distribution confirmed with the Kolmogorov-Smirnov test. Comparisons of the changes in the frequencies of the ranges of antibody determinations according to each specific cut-off point from 4-5 to 8-9 months were performed with the Pearson's chi-squared test or Fisher's exact test. Comparisons of changes in IgG measured in BAU/ml compared to RBD from 4-5 to 8-9 months, in general, and stratified by COVID-19 severity were performed with the Wilcoxon test for paired samples. Comparison of these same determinations for the same period according to COVID-19 severity was performed with the U Mann-Whitney test. All hypothesis contrast tests were bilateral at a significance level $P \leq 0.05$ and the calculations involved were performed with the support of the SPSS 25.0™ statistical data processing package from IBM Co®.

Results

A total of 72 patients who met the inclusion criteria and gave their consent participated in the study. The total sample of participants had an age of 63 (13) years in a range of 32-89 years, 53% were women. Seventy-nine percent of the patients showed pre-existing chronic comorbidities. The distribution of comorbidities was as follows: 56% hypertension, 39% type 2 diabetes, 19% chronic pulmonary disease, 15% heart disease, 10% chronic kidney disease, 7% oncologic disease and 1% cerebrovascular disease. A total of 75% had 2 or more comorbidities. Some 36% were smokers or former smokers. The degree of clinical severity of COVID-19 was rated as mild in 6%, moderate in 58% and severe in 36%. Ninety-three percent of the patients with pre-existing chronic comorbidities, had moderate and severe COVID-19. Patients were hospitalized in different departments: 54% in Internal Medicine-Infectious Diseases, 25% in Pneumology, 18% in Intensive Care Units and 3% in Home Hospitalization Unit. Hospital stay was 13 (1-41) days. The duration of the acute phase was 23 (8-62) days. During the acute phase of the disease, 93% developed pneumonia. Forty-nine percent required no ventilatory support, while 25% required high-flow nasal spectacles, 13% noninvasive mechanical ventilation and 13% invasive according to the severity of the process. In

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cases with moderate and severe COVID the oxygen saturation during admission was 91 (4) % in a range of 70-98%. Clinical follow-up due to post COVID-19 pulmonary sequelae was finished in 87% of patients after one year, and clinical follow-up time by the Multidisciplinary Unit of Interstitial Lung Diseases of the Hospital was 8 (1-12) months. Of the total patients, forty percent had pulmonary sequelae, including seventeen percent with minimal parenchymal alterations with no clinical or functional repercussions, three percent with had ground-glass infiltrates and twenty percent mild with pulmonary fibrosis. Forty of the 72 patients participated in the antibody analysis; 20 attended the sample collection for antibody determination at 4-5 months and at 8-9 months post COVID-19 and another 20 at 8-9 months post COVID-19. All of them had moderate or severe COVID, and thirty six percent had minimal parenchymal sequelae with no clinical or functional repercussions, and none developed pulmonary fibrosis. The results of the humoral response to SARS-CoV-2 at 4-5 months and 8-9 months post Covid-19 infection are shown in Table 1.

Positivity to the combination of IgG RBD, IgA Spike and IgM Spike was 25% at 4-9 months and 23% at 8-9 months. The difference in IgM Spike 1 from 4-5 months to 8-9 months reached significance (p=0.009), while the difference in IgA Spike 1 between the two periods reached marginal significance (p=0.053). The differences of IgG Nucleocapsid and IgM Nucleocapsid did not reach statistical significance. The amount of IgG RBD antibody was 111.9(11.3-642.7) BAU/ml in the period 4-5 months post COVID-19 d 111.8(21.2-1820) BAU/ml in the period 8-9 months post COVID-19 (p=0.391). The amount of RBD IgG antibodies produced at 4-5- and 8-9-months post-infection according to the degree of severity of the COVID-19 disease suffered are shown in Table 2. No statistical significance was found for their differences either within or between periods.

To date (February 2022) we have not detected any case of re-infection requiring a microbiological diagnosis in our study.

Discussion

This paper presents a study of patients with a microbiological diagnosis of SARS-CoV-2 infection who required hospital admission. A high percentage of these patients had pre-existing chronic comorbidities and all of them suffered a moderate or severe course of the disease. Different studies have related the severity of COVID-19 infection with previous the comorbidities presented. We found that hypertension and type 2 diabetes were the main diseases, coinciding with other authors such as Huang et al. [10]. Half of the patients required respiratory support measures: 25% with high-flow nasal spectacles, 13% noninvasive ventilation and 13% of patients required IMV, a higher percentage than in other series [11]. Prolonged exposure to high concentrations of oxygen is known to result in heightened production of oxygen-derived free radicals which can damage the pulmonary epithelium [12]. After a one year follow-up, forty percent of patients had pulmonary sequelae, exactly 23% with clinical or functional repercussions, something similar was demonstrated by Cocconcelli et al. [13], who found that 20% of patients showed persistent lung abnormalities at 6 months after hospitalization for COVID-19 pneumonia. On the other hand, Huang C et al. [11], described that most patients (76%) are symptomatic to some degree after six months of COVID-19 infection, the most common symptomatology being fatigue and muscle weakness in 63%, insomnia in 26% and anxiety in 23%. Pulmonary function impairment was

Table 1: Humoral response to SARS-CoV-2 at 4-5 months and 8-9 months after Covid-19 infection.

DETERMINATION n(%)	At 4-5 months post infection				At 8-9 months post infection			
	POSITIVE	NEGATIVE	UNDET.	INDEX median (min-max)	POSITIVE	NEGATIVE	UNDET.	INDEX median (min-max)
IgG RBD	20 (100)	0 (0)	---	---	40 (100)	0 (0)	---	---
IgG nucleocapsid	16 (80)	1 (5)	3 (15)	3.8 (0.6-8.6)	19 (47.5)	16 (40)	5 (12.5)	1.2 (0.1-6.6)
IgM Spike1	5 (25)	15 (75)	---	0.2 (0.0-4.7)	9 (22.5)	31 (77.5)	---	0.2 (0.0-4.2)
IgA Spike1	18 (90)	0 (0)	2 (10)	3.2 (0.8-5.5)	35 (87.5)	0 (0)	5 (12.5)	3.7 (0.8-10)
IgM nucleocapsid	1 (5)	1 (5)	18 (90)	0.3 (0.0-1.8)	1 (2.5)	36 (90)	3 (7.5)	0.2 (0.0-2.8)

Table 2: Amount of RBD IgG Ab measured in BAU/ml as a function of disease severity, at 4-5 months and at 8-9 months post COVID-19 infection.

COVID SEVERITY	IgG RBD positive		IgG (BAU/ml) median (min-máx)		P-Value
	at 4-5 months	at 8-9 months	at 4-5 months	at 8-9 months	
MODERATE n (%)	9 (45)	22 (55)	91.3 (43.9-577.9)	130.9 (24.7-1,820)	0.441
SEVERE n (%)	11 (55)	18 (45)	148.4 (11.3-642.7)	94.6 (21.2-1,123.4)	0.594
P-Value	---	---	0.503	0.251	---

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also reported in 22 to 56% of cases, being higher in those cases that had more severe cases of COVID-19 disease during the acute phase. Very similar results were obtained by Lombardo et al. [14], one year after SARS-COV-2 infection in hospitalized patients, reaching a pulmonary involvement of 37%. They found that interstitial thickening and ground-glass infiltrates were the most frequent form of pulmonary sequelae. However, pulmonary fibrosis is exceptional and risk factors for its development are considered to be age, severity of COVID-19 disease, prolonged stay in ICU, need for mechanical ventilation, smoking and alcoholism [15]. In our study, most patients that had mild pulmonary fibrosis suffered severe COVID-19 during the acute phase. Of the 40 patients who participated in the antibody analysis all presented RBD IgG after 8-9 months post COVID-19 infection, which is consistent with previously published studies [16]. In addition, 47% of patients were positive for IgG Nucleocapsid and 2.5% for IgM Nucleocapsid, coinciding with other studies such as Ripperger et al. [17], where they report that Nucleocapsid antibodies decrease more rapidly than RBD antibodies. Likewise, 88% presented positivity to IgA Spike, coinciding with other studies such as that of Dan et al. [18] which also detects it in serum in the majority of subjects 6-8 months after infection. Twenty-three percent of patients were positive for RBD IgG, Spike IgA Spike and RBD IgM, which could contribute to a greater capacity to neutralize the virus in these patients [19] and avoid new reinfections. In the analysis of the evolution of antibodies from 4-5 months to 8-9 months we found no difference in the amount of RBD IgG detected, so that similar levels of Spike IgG were maintained in both periods of convalescence analyzed, something already observed in other studies [18,20]. However, we did find a significant decrease in Spike 1-RBD IgM, coinciding with other authors such as Gaebler et al. [6]. It has been described in the literature that during the acute phase of the disease there are higher levels of IgG to S1 and Nucleocapsid in patients with severe COVID-19 than in those with milder disease [5,6]. However, in our study we did not find differences when the level of RBD IgG according to the severity of the COVID-19 disease suffered was compared, coinciding with other authors such as Sandberg et al. [20], probably because all our population had a diagnosis of pneumonia and were stratified as severe or moderate COVID-19, without having patients with mild or asymptomatic disease, as well as the period after the COVID-19 infection analyzed. On the other hand, we observed that the amount of RBD IgG antibodies is maintained throughout the convalescent COVID-19 phase and that the amount that remains in the medium term seems to protect against new reinfections. Finally, we believe that the development or not of pulmonary fibrosis is probably independent of the amount of RBD IgG generated, since we observed that regardless of the level of antibodies maintained, a considerable proportion of COVID-19 patients developed discrete interstitial parenchymal alterations. There are some limitations to this study. The first one is that the sample size is small, which undermines the power of the study. On the other hand, in our study the majority of patients suffered a moderate-severe degree of severity of the disease, who were those who required follow-up by the multidisciplinary consultation, so that the humoral immune response profile cannot be applied to patients with a mild degree of severity or to asymptomatic patients. In our study twenty percent of patients had mild pulmonary fibrosis but we did not considered all patients with any kind of risk factor associated at pulmonary fibrosis like persistent systemic inflammation. Taking these limitations into consideration, our study describes that amount of RBD IgG does not seem to predict the development or not of pulmonary fibrosis in patients at risk of pulmonary fibrosis Post Covid-19.

Ethical Approval Statement

The study was approved by Ethical Committee with the code CHUC_2020_68.

Conflict of Interests

The authors declare no competing interests.

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