Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

[d] Section of Respiratory Medicine, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Spain
[e] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Spain
[f] Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
[g] Esteve Teijin, Barcelona, Spain
[h] Quantitative Methods Department and TiDES Institute, Las Palmas de Gran Canaria University, Las Palmas de Gran Canaria, Spain
[i] Esteve Teijin, Zaragoza, Spain
[j] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[k] Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, Spain
[l] CIBER de Epidemiologia y Salud Pública, Madrid, Spain
[m] Agency for Health Quality and Assessment of Catalonia (AQuAS), Barcelona, Spain

* Corresponding author.
E-mail address: jmmontserrat@ub.edu (J.M. Montserrat).

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Influence of Cytokine Release Syndrome in Severe COVID-19 Patients Treated With Tocilizumab Over the Quantiferon TB Gold Plus Results

Influencia de la tormenta citoquímica de pacientes COVID-19 graves tratados con tocilizumab sobre los resultados del Quantiferon TB Gold Plus

Dear Editor,

During the first COVID-19 peak and after administering it to approximately 500 patients in Wuhan,[1] the Chinese health authorities included tocilizumab (TCZ), an interleukin 6 receptor antagonist, for the treatment of severe SARS-CoV-2 pneumonia.

With increasing evidence of its effectiveness in severe COVID-19,[2] in Spain the Ministry of Health authorizes TCZ expanded access, prioritizing the inclusion of patients in clinical trials.[3,4] As it is an immunosuppressive agent, it is advisable to screen for latent infections caused by intracellular bacteria, parasites and viruses, such as *M. tuberculosis*, which could be reactivated during treatment with TCZ[5] in patients who may be candidates to receive it for long periods. Additionally, a recent, non-peer-reviewed report indicates that, like pandemic influenza, SARS CoV-2 might increase the number of tuberculosis (TB) cases and related mortality.[6] Moreover, new cases of coinfection TB-COVID-19 have been drescribed.[7] Finally, several original works, reviewed during the first European congress on SARS CoV-2 (ECCVID) held online between September 23 and 25, 2020, coincide in stating that mortality is influenced by SARS CoV-2, as much in patients with a history of TB as in those with active TB.[8]

From March 15 to May 15 2020, an IGRA test, Quantiferon TB Gold Plus (QFN-Qiagen, Venlo, The Netherlands), was requested[9] in our hospital for patients with SARS CoV-2 confirmed by PCR who met clinical (on the COVID-19 severity scales), radiological (new onset or progression of the initial pulmonary infiltrates) and biological (IL-6 > 40 pg/ml) criteria for treatment with TCZ in order to evaluate their immune response to latent tuberculosis infection (LTBI) before starting TCZ. Additional blood tests were done to examine other immune parameters, including CD4+ and CD8+ lymphocyte counts. Patients gave their verbal consent before undergoing treatment and for the use of their clinical data and storage of surplus samples in a biological bank (biobank) for research purposes. Both approval of the Hospital Pharmacy Committee and authorization from the Research Ethics Committee were obtained before treatment began.

Among the 190 patients treated with TCZ, the mean age (±SD) was 59.7(19.6) years and 125 (71%) were male. Seventy-two (38%) required ventilation in Intensive Care (ICU). Twenty-two (30% of those requiring ventilation) and 7 (6% of the non ICU patients) died as a result of refractory distress (ARDS). Valid samples for QFN were obtained in 119 patients (63%). The results were negative in 67 (56.3%), indeterminate in 48 (40.3%) and positive in 4 (3.4%). Upon retesting the patients with indeterminate results after 8 weeks, all but one who tested positive had negative results. The CD4+ and CD8+ counts extracted prior to TCZ administration showed a median of 321 cells/mL (IQR: 49–1356) and 171 (IQR: 16–1083), respectively. There were no differences in these T-lymphocyte counts between patients admitted and not admitted to the ICU (Table 1).

These data illustrate that SARS CoV-2, while producing an exacerbated inflammatory response, may be associated with T-lymphocyte depletion-dysfunction, which may reduce the capability of Quantiferon TB Gold Plus to identify the LTBI response in patients with moderate and severe COVID- 19. In our cohort, severe COVID-19 patients with cytokine release syndrome, showed medians of CD4+ and CD8+ below 350 and 200 cells/mL, respectively, which were probably the cause of the higher-than-expected indeterminate QFN values (40.3%). Similar results have been seen in several IGRA-based LTBI studies in immunosuppressed individuals.[10,11]

Since SARS CoV-2 could influence the dynamics of *M. tuberculosis*, specific follow-up of recovered COVID-19 patients at high risk factors of developing active TB should be considered independently of the results of QFN.

Table 1
Demographic data and results of Quantiferon and CD4+/CD8+ counts in patients receiving TCZ.

	TCZ (*N*)	Mean age (±SD)	Sex (*N*)		T cell (median)*		Quantiferon *N* (%)			Exitus (%)
			M	F	CD4+	CD8+	Pos	Neg	Ind	
ICU admitted	72	59.3 (±22.6)	46	26	293	129	2 (6)	20 (59)	12 (35)	22 (30)
Non ICU	118	60.0 (±10.6)	79	39	347	191	2 (3)	47 (55)	35 (41)	7 (6)
Total	190	59.7 (±19.6)	125	65	321	171	4 (3.4)	67 (56.3)	48 (40.3)	29 (15)

Glossary: ICU = Intensive Care Unit; *N* = cases; M = male; F = female; Pos = Positive; Neg = Negative; Ind = Indeterminate. **P* value non significant between ICU and non ICU (>0.05).

Appendix A. COVID-19 Infectious Disease Team Hospital del Mar are:

Itziar Arrieta, Joan Gómez-Junyent, Silvia Gómez-Zorrilla, Alicia González, Ana Guelar, Roberto Güerri, Elisabeth Lerma, Emili Letang, Inmaculada López-Montesinos, María Milagro Montero, Nuria Prim, Helena Sendra, Ana Siverio, Luisa Sorlí, Judit Villar and Juan Pablo Horcajada.

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Francesca Sánchez-Martínez, Mar Arenas-Miras*, Neus Jové-Caballé, Hernando Knobel-Freud, on behalf of COVID-19 Infectious Disease Team Hospital del Mar[1]

Infectious Diseases Service, Hospital del Mar, Barcelona, Spain

* Corresponding author.
E-mail address: mariadelmararenasmiras@gmail.com
(M. Arenas-Miras).
[1] Please see a list of the members of the COVID-19 Infectious Disease Team Hospital del Mar in Appendix A.

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Lung Function *sequelae* in COVID-19 Patients 3 Months After Hospital Discharge

Secuelas en la función pulmonar de los pacientes con COVID-19 tres meses después del alta hospitalaria

Dear Editor:

About 20% of patients infected by the SARS-CoV-2 virus develop Coronavirus Disease 2019 (COVID-19) pneumonia and require hospitalization.[1] Some recent reports have shown that some of them may present lung function abnormalities at discharge,[2,3] or soon afterwards.[4–6] Here, we: (1) describe the presence and characteristics of lung function abnormalities 3 months after hospital discharge in a large prospective cohort of well characterized patients hospitalized because of COVID-19 in our institution; and, (2) explore potential clinical predictors these short-term lung function *sequelae*.

We included in the study 172 patients discharged from Hospital Clinic in Barcelona because of COVID-19 pneumonia from 4th of March to 27th April 2020. The study protocol was approved by our Ethical Review Board (HCB/2020/0422), and all patients signed their informed consent. Demographic, clinical and biological characteristics were recorded on hospital admission and 3 months after discharge. All patients followed the current Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) consensus for post-COVID-19 clinical follow-up.[7] The severity of COVID-19 was classified as *moderate* in patients who did not require supplemental oxygen and *severe* in those who did, according to WHO recommendations.[8] Spirometry and carbon monoxide lung diffusion capacity (DLCO) were measured (Medisoft, Sorinnes, Belgium) following international recommendations[9,10] 3 months after hospital discharge adapted to current pandemic situation.[11,12]

Mean age was 56.1 ± 19.8 years-old and 57% of patients were males. Hypertension (37%) and diabetes (16%) were frequent prior comorbid conditions. Most patients (70%) had severe COVID-19 and 43% were admitted to the intensive care unit (ICU). Length of stay in ICU was 14.6 ± 27.3 days and in hospital 20.1 ± 16.3 days. On average, 3 months (101.5 ± 19.9 days) after discharge spirometry was normal (median [interquartile range] FEV_1 94 [80–105]%, FVC 90 [80–100]% of predicted and FEV_1/FVC ratio 0.80 [0.75–0.84]) but DLCO was slightly reduced (77 [64–88]% of predicted). Yet, a more granular analysis showed that 109 patients (63%) had evidence of altered pulmonary function at 3 months of follow-up, as defined by values of FEV_1, FVC and/or DLCO < 80% of reference. The most frequent abnormality was reduced DLCO (98 patients (57%)), followed by low FEV_1 (43 patients (25%)) and low FVC (42 patients (24%)).

Table 1 compares the main characteristics of patients with normal and abnormal DLCO values 3 months after discharge. We observed that: (1) the later included more smokers and patients with hypertension, diabetes, cardiovascular disease or chronic obstructive pulmonary disease (COPD); (2) on admission, these patients showed higher levels of D-dimer, lactate dehydrogenase (LDH), and creatinine (and reduced platelet counts); (3) during hospitalization, differences in WHO severity of disease failed to reach statistical significance, but the prevalence of acute respiratory distress syndrome (ARDS) and pulmonary embolism was higher in patients with reduced DLCO after discharge. These patients also showed prolonged ICU and hospital stay; and, finally, (4) 3 months after discharge, patients with reduced DLCO were more dyspnoeic and showed higher values of C-reactive protein (CRP), LDH and creatinine (Table 1).