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.

5. Dribin TE, Michelson KA, Zhang Y, Schnadower D, Neuman MI. Are children with a history of asthma more likely to have severe anaphylactic reactions? A retrospective cohort study. *J Pediatr*. 2020;220:159–164.e2.
6. Turner PJ, Baumert JL, Beyer K, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy*. 2016;71(9):1241–1255.
7. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130(6):1260–1274.
8. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med*. 2012;367(3):233–243.
9. Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization systemic allergic reaction grading system: is modification needed? *J Allergy Clin Immunol Pract*. 2017;5(1):58–62.e5.
10. Muraro A, Fernandez-Rivas M, Beyer K, et al. The urgent need for harmonized severity scoring system for acute allergic reactions. *Allergy*. 2018;73(9):1792–1800.

Positive outcome in a patient with coronavirus disease 2019 and common variable immunodeficiency after intravenous immunoglobulin

We present a case of a patient with immunodeficiency who has recovered from coronavirus disease 2019 (COVID-19). The patient is a 53-year-old woman who received a diagnosis of common variable immunodeficiency in 1996 and has been on regular intravenous immunoglobulin (IVIG) replacement therapy with Gamunex-C 40 g (520 mg/kg/dose) every 2 weeks. The last immunoglobulin G trough level was 1478 mg/dL on November 12, 2019, and a high-dose influenza vaccine was administered in September 2019. The patient also has hypothyroidism, bronchiectasis, and Sjogren's syndrome treated with hydroxychloroquine 400 mg daily. Her last chest computed tomography (CT) scan in March 2018 revealed mild central bronchiectasis. On March 13, 2020, the patient received her routine scheduled IVIG infusion, and on March 16, 2020, the patient reported that her spouse was in contact with a patient with COVID-19 and that he was feeling ill.

The patient presented to the emergency department on March 17, 2020, with complaints of fever, chills, productive cough, shortness of breath, nausea, vomiting, and diarrhea. She appeared well on admission without evidence of respiratory distress. Her chest CT scan revealed multifocal, bilateral, patchy, and confluent ground-glass opacities with interlobular septal thickening and microvascular dilatation sign—all characteristic of the COVID-19 pulmonary infection.

Initial laboratory results revealed leukopenia (lymphopenia), normal coagulation profile, electrolytes, and liver function. Influenza/respiratory syncytial virus panels were negative. The patient was admitted to a regular nursing floor and started receiving ceftriaxone and doxycycline. At this time, we decided to administer another 40-g dose of IVIG.

On day 2 of hospitalization, she required 2 L/min oxygen by nasal cannula. On day 5, the patient had an increased oxygen requirement and was transferred to the intensive care unit. Her respiratory status worsened and needed escalation of support to noninvasive positive pressure ventilation/continuous positive airway pressure, and ultimately, intubation and mechanical ventilation on hospital day 7. Her medical treatment included ceftriaxone and doxycycline for the duration of hospitalization and hydroxychloroquine, which was increased from her home regimen to 600 mg/d. She was successfully weaned and extubated on hospital day 13. On day 14, the second dose of 40-g IVIG was administered, after which, the patient was discharged home to self-quarantine owing to a positive repeat COVID-19 testing. The patient never received any convalescent COVID-19 plasma.

The underlying pathophysiology of COVID-19 is under investigation in animal models. It seems that the virus induces an inflammatory response involving macrophage hyperactivation, leading to a cytokine storm responsible for severe lung and systemic complications, making IVIG's anti-inflammatory effect potentially useful in treating COVID-19,[1,2] especially in cases of severe COVID-19 associated with lymphopenia and increased cytokine levels.[3]

We present a case of COVID-19 at a very high risk for morbidity and mortality secondary to underlying immunodeficiency and bronchiectasis. Despite presenting with classical pneumonia requiring intubation and mechanical ventilation, the patient recovered completely and had a relatively short hospital course. Patients who have had similar courses had a reported mortality rate of 49% to 97%.[4,5] It is hard to ascertain if this was a result of the hydroxychloroquine, high-dose IVIG, or a combination of both. In addition, IVIG has been shown to have an immunomodulatory, anti-inflammatory effect especially if given in higher doses. The exact mechanism is still unknown, but it has been suggested that it occurs through an Fc-mediated mechanism or Fab-mediated mechanisms.[6] Azithromycin was not included in the patient's therapy owing to a history of allergic reaction to the antibiotic. Hydroxychloroquine has been found to be associated with viral load reduction/disappearance and its effects reinforced by azithromycin in a small group of patients[7] However, its efficacy in improving clinical course is yet to be determined.

Our findings suggest that the early administration of IVIG may be beneficial in improving the outcome of this illness, especially in patients with an immunodeficiency disorder. A similar report of 3 patients from the People's Republic of China noted that high-dose IVIG had a significant impact on improving symptoms, fever curve, and lymphopenia,[8] although the selected patients in that report were not immunodeficient. We speculate that IVIG, in addition to its immunomodulatory effect, may contain antibodies to other coronaviruses that are cross-reactive with COVID-19. This might lead to modulation of the severity of the illness similar to what is observed in the pediatric population who, in general, present with a milder form of this disease that is speculated to be secondary to previous exposure to other coronavirus infection.

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References

1. Ferro F, Elefante E, Baldini C, et al. COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol*. 2020;38(2):175–180.
2. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–1034.
3. Pedersen SF, Ho Y-C. SARS-CoV-2: a storm is raging. *J Clin Invest*. 2020;130(5):2202–2205.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention [e-pub ahead of print]. *JAMA*. https://doi.org/10.1001/jama.2020.2648.
6. Nagelkerke SQ, Kuijpers TW. Immunomodulation by IVIg and the role of Fc-gamma receptors: classic mechanisms of action after all? *Front Immunol*. 2015;5:674.
7. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial [e-pub ahead of print]. Int J Antimicrob Agents. https://doi.org/10.1016/j.ijantimicag.2020.105949.
8. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect Dis*. 2020;7(3):ofaa102.

Sputum vitamin D binding protein

A potential biomarker of airway vitamin D axis in asthma

The vitamin D (VitD) axis, which includes VitD, VitD-binding protein (VDBP), and the VitD receptor, has been found to regulate immunomodulatory functions that may be of particular relevance in asthma.[1] Serum VitD is the most typically used surrogate of the VitD axis to explore the impact of the axis on clinical asthma expression. However, the findings are controversial.[2]

Currently, Gupta et al[3] reported that VDBP concentration in bronchoalveolar lavage fluid (BAL), but not serum, was markedly higher in therapy-resistant children with severe asthma and was inversely correlated with asthma severity. Little is known whether serum surrogates of the VitD axis levels could accurately represent their airway counterparts to reflect the local immunomodulatory effects in the lung. In this study, we measured VitD and VDBP levels in matched serum and sputum supernatant in adult patients with asthma and compared the difference in clinical relevance. Although BAL provides insight into the pathophysiology of asthma, a major disadvantage is the invasiveness of the procedure, precluding frequent sampling in the same subject. Induced sputum method has been proposed as a noninvasive alternative to bronchoscopy for investigating local airway inflammation at follow-ups.

A total of 203 patients with asthma were recruited for our study from the Department of Allergy and Clinical Immunology at The First Affiliated Hospital of Guangzhou Medical University from December 2017 to February 2019. All subjects underwent a standardized clinical assessment, including pulmonary function test, sputum inflammatory cell differentiation, allergy status (serum-specific immunoglobulin E measurement), fractional exhaled nitric oxide measurement, and complete blood cell count. Sputum induction was performed successfully for 124 subjects, of whom 96 had an adequate volume of sputum supernatant after sample processing for further measurement. The processing of sputum induction and sputum sample normalization were described in our previous study.[4] All subjects included in this study had received a treatment recommended by the Global Initiative for Asthma guidelines and did not take VitD supplements for at least 6 months before recruitment. The study was approved by the Ethics Review Board of the First Affiliated Hospital of Guangzhou Medical University (Medical ethics year 2017 No. 25). All participants provided written informed consent. The VDBP levels in serum and sputum were measured using enzyme-linked immunosorbent assay (Research and Development Systems, Minnesota), and VitD (25-hydroxyvitamin D3 [25-(OH)D_3]) levels were measured by our hospital laboratory department using Roche Modular E170.

Sputum VDBP concentrations were significantly lower in patients with mild asthma than in patients who have moderate or severe asthma ($P < .001$, and $P < .001$), and there was no difference among the groups with differing asthma severity regarding the concentrations of either serum 25-(OH)D_3 or serum VDBP. In addition, the sputum VDBP concentrations of subjects with airway eosinophilia were significantly higher than in subjects without airway eosinophilia ($P = .03$). The levels of 25-(OH)D_3 were not detectable in our sputum samples. Sputum VDBP negatively correlated with lung function indices, including forced expiratory volume in 1 second % ($r = -0.341$, $P = .002$) and forced expiratory flow between 25% and 75% ($r = -0.286$, $P = .01$), and positively correlated with sputum eosinophil count ($r = 0.280$, $P = .01$). However, we did not observe a correlation between serum VDBP or serum VitD with any clinical parameter. There was no association between sputum VDBP and serum VDBP ($r = 0.095$, $P = .57$) or between sputum VDBP and serum VitD ($r = 0.161$, $P = .32$), and serum VDBP and serum VitD ($r = 0.220$, $P = .38$) (Fig 1).

Our study is the first to compare the clinical relevance of the surrogates of the VitD axis in matched serum and sputum samples. Although sputum 25(OH)D_3 was not detectable, we found that patients with mild asthma had lower sputum VDBP levels than patients with moderate and severe asthma. In addition, sputum VDBP concentrations were substantially correlated with lung function indices and airway eosinophilia. A similar degree of clinical relevance was absent for both serum 25(OH)D_3 and serum VDBP. These data revealed that sputum surrogates of the VitD axis might be more relevant in asthma characteristics than their serum counterparts.

Furthermore, VDBP is a critical component of the VitD axis and has immunomodulatory functions relevant in a range of lung diseases, including chronic obstructive pulmonary disease, tuberculosis, and asthma, predominantly relating to macrophage activation and neutrophil chemotaxis.[5] Bratke et al[6] reported that a marked increase in VDBP in human BAL 24 hours after allergen challenge and the increased VDBP levels were markedly correlated with eosinophils in BAL, suggesting a role of VDBP in late-phase asthma.[6] Our findings reveal that increased sputum VDBP concentrations might be a risk factor of asthma severity through contributing to airway eosinophilia and decreased lung function, which are 2 dominant features of asthma. One possible interpretation of the

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