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.

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Letter to the Editor

Letter to the Editor in response to the article "Could IL-17 represent a new therapeutic target for the treatment and/or management of COVID-19-related respiratory syndrome?"

Dear Sir,

In recently published letter, Casillo, Mansour et al. reported that IL17 could represent a new therapeutic target for the treatment and management of COVID-19-related respiratory syndrome [1].

In a recent work focused on COVID-19 severe manifestations cytokines, Henderson et al. stated that early intervention is essential to avoid irreversible tissue damage, and that a treatment with glucocorticoids, IVIG, and/or anti-cytokine therapies should be early considered, with the aim of reverting the hyperinflammation status, before ARDS (Acute Respiratory Distress Syndrome, one of the main concerns in COVID-19 patients) occurs [2]. Interestingly, they did not take into account IL17 role, which should be, in our opinion, better defined.

Current therapeutic approaches includes drugs to manage the hyperinflammatory status, as tocilizumab, a monoclonal anti IL-6 antibody [3] and corticosteroids [4] and drugs that shows an anti-viral activity, such as chloroquine and hydroxychloroquine [4], lopinavir/ritonavir [4] (with recent findings by Cao et al. reporting no clinical benefit beyond standard care) and remdesivir [4].

In a recent meta-analysis Hu et al. reported that ARDS and ACI (Acute Cardiac Injury) are the main obstacles for patients to treatment recovery [5]. This represents an interesting link with previous studies that report a large involvement of IL17 in the genesis of acute lung injury from various causes, and with studies on murine models that demonstrated a lowering of IL17 and other inflammatory cytokines in viral myocarditis when controlled by therapy [6].

There is also a strong connection between the present pandemic COVID-19 disease, and the acute lung injury induced by the past 2009 pandemic Influenza A (H1N1) Virus [7]. First, previous clinical reports indicated that hypercytokinemia was involved in the pathogenesis of severe 2009 pandemic Influenza manifestations [7]. In a panel of 24 cytokines, IL17 was elevated in all mild, hospitalized and critical patient, and Th17 mediators (IL6, IL8, GCSF and GMCSF) were also elevated, suggesting that IL17 may play an important role [7]. Moreover, C. Li et al. demonstrated that IL17 deficiency, or treatment with monoclonal antibodies targeting IL17, ameliorated acute lung injury in a mouse model of H1N1 virus lung damage [7].

All these results are in line with what reported in the recent letter by Casillo, Mansour et al., with the COVID-19 infection model that, in severe cases, lead to the release of IL-6, IL-1β and tumor necrosis factor-α (TNF-α), which contribute to lung damage by further aggravating clinical features such as pneumonia severity [1].

Giving that diffuse alveolar damage (DAD) is the histological hallmark of ARDS, characterized by hyaline membranes, intra-alveolar oedema, alveolar epithelial cell injury, and neutrophilic inflammation, M.Buttignol et al. in 2017 have found that this histological pattern is found in all lung parenchyma samples of patients affected by severe pulmonary manifestations of H1N1, and that IL17 is very high in the small airways of patients who died of ARDS due to the virus H1N1, as for deceased patients from other causes ARDS [8]. Together with the studies cited above, these findings would seem to place IL17 at the center of a model of acute lung injury from various causes. Lung tissues from patients deceased for influenza A(H1N1) presented also a marked cytotoxic infiltrate, with increases in CD8 + T cells, NK + cells and granzyme A + cells in the parenchyma [8].

C. Mikacenic et al. reported a strong correlation between the presence of IL17 in BAL patients with various aetiology ARDS and higher bronchoalveolar lavage percent neutrophils and total protein concentration. Elevated interleukin-17A was associated with higher Sequential Organ Failure Assessment scores, and they concluded that IL17 is strongly associated with alveolar permeability and organ dysfunction in acute respiratory distress syndrome. Authors also found that serum IL17 correlated with an increased risk of death at 28 days in patients with ARDS (excluding patients with trauma), the association remained statistically significant also after adjustment for differences in age, gender, and ARDS risk factor of sepsis (1.45 [1.12–1.88]; $p = 0.005$) [9].

Y. Zhi-xin reported also that within 24 h after the onset of various origin ARDS (carefully excluding paediatric patients, patients with known history of cancer, end-stage liver or renal disease, and chronic immune-mediated disorders/patients under steroids or NSAIDs therapy, or who died within 24 h of receiving a diagnosis of ARDS) the peripheral circulating Th17/Treg cell ratio gradually increased from mild to severe ARDS. Th17/Treg ratio could be positively correlated with APACHE II score, SOFA score, and Lung Injury Score, while there was a negative correlation with PaO2/FiO2 index. Moreover, ARDS patients with a Th17/Treg ratio > 0.79 had higher 28-day mortality ($P < 0.001$), with a sensibility of about 875% (better than APACHE II score and SOFA score alone). The authors concluded that Th17/Treg imbalance, favoring a Th17 shift, could represents a potential therapeutic target to alleviate lung injury and a novel risk indicator in patients with early ARDS [10].

In a murine model Q. Li et al. confirmed these findings, with also a correlation between IL17 BAL concentration and body weight loss; moreover, neutralization of IL17 by monoclonal antibodies significantly abrogated lung damage of ALI mice. In the same work, IL17 serological levels were also positively correlated with IL6 and VEGF levels in ARDS patients (n. 20 patients). Again, the authors indicated IL17 as a novel potential therapeutic target in ARDS patients [11].

On these basis, in a similar murine model Y.S. Chai et al. found that IL38 alleviates lung injury in ARDS, probably preventing naïve T cells differentiating to Th17 cells (the main IL17 producers). They stated that specific mechanisms need further exploration, and rely on the IL-1, IL-6, STAT3, RORγt and downstream metabolic pathway of mTOR [12].

The proposal of Casillo, Mansour et al. of targeting IL17 seems very reasonable, with the aim to controlling an overly activated immune mechanism. Apart from the just cited evidences, Hot and collaborators, show

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that IL17 is able, especially if expressed together with other inflammatory cytokines, to mediate a procoagulative state in human endothelial cells [14]. This procoagulative state is very often found in COVID-19 patient, that are at increased venous thromboembolism risk [14].

IL-6 and TGF-β initiate Th17 cell differentiation by activating STAT3. Th17 cell population maintenance and expansion can also rely on IL-23 and on autocrine secretion of IL21 (via STAT3 activation) [16]. Also IL1β and IL23 are sufficient (together) to induce human Th17 cells from CD4+ naive T cells [16].

IL17 is considered one of the main components of the respiratory tract immune system and can stimulate the production of a great number of chemokines/cytokines, adhesion molecules, leading to strong neutrophils recruitment [15].

So, blocking STAT3 as suggested [1], could result in a considerable therapeutic advantage in patients with severe pulmonary manifestations from COVID-19; however, it could lead, in a clinical situation where rapid action is required, to a slower therapeutic response (requiring various interactions to achieve a therapeutic effect and not blocking circulating IL17) compared to direct blocking of the cytokine. STAT3 inhibitor fedratinib has an unfavourable side effects profile (including thrombocytopenia, that is already common in COVID-19 patients, neutropenia, ALT, AST, bilirubin elevation, and Wernicke's encephalopathy), and more drug interactions (interacts with CYP3A4 inducers/inhibitors and with CYP2C19 inhibitors), compared with IL17 or IL17RA direct inhibitors (monoclonal antibodies) which could quickly stop the lung injury process from early stages, safely.

It is interesting to note that of the three commonly used IL17 inhibitors (ixekizumab, secukinumab, brodalumab), we have more data about intravenous administration, the preferred route when rapid onset of action is required, only for one (secukinumab [17]), and all have respiratory tract infections as main side effect [18], so they would seem to have a consistent effect precisely in the tissue and context required by the current COVID-19 pandemia. Furthermore, data on the clinical use of secukinumab during pregnancy would seem reassuring [19, 20]. There are no equally consistent data for the other mentioned molecules.

Therefore it would be of great interest measuring IL17, IL6 and the other main inflammatory cytokines plasma levels in covid-19 hospitalized patients, to look for a correlation with other ARDS typical clinical parameters. On the other hand it would be of paramount interest to check how patients already on IL17 inhibitors treatment (for other clinical indications) react to the SARS-CoV-2 infection. In a recent retrospective multicenter observational study including 5206 patients with chronic plaque psoriasis being treated in northern Italy (the area with the highest number of COVID-19 related deaths in the country) with biologic therapy and also with anti IL17 monoclonal antibodies, Gisondi et al. reported no cases of deaths from COVID-related disease, 4 out of them required medical assistance in an hospital for COVID-related disease. The only patient treated with anti IL17 (secukinumab) did not required intensive care unit assistance, and was hospitalized for 12 days in internal medicine unit and fully recovered [21]. These results are not statistically significant, but indicate the urgent need for further studies.

In a short time, it would be very important to create trials involving the use of direct IL17 inhibitors.

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Declaration of Competing Interest

The authors, Gabriele Ceccarelli, Katiuscia Nardi and Francesca Marchesani, declares no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.104933.

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