



# COVID-19: An Acute Secondary Interferonopathy? The Mirror of Autoinflammatory Syndromes

Julián Fernández-Martín<sup>1\*</sup>, Pérez-Álvarez Roberto<sup>1</sup> and Lamas-Barreiro José María<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Hospital Álvaro Cunqueiro, Spain

<sup>2</sup>Nephrology Service, Hospital Álvaro Cunqueiro, Spain

## Abstract

Between 1 and 2% of SARS-CoV-2 infected patients develop a devastating acute systemic inflammatory syndrome with predominantly pulmonary expression. Clinical data, analytical findings and the few pathological references we have so far suggest SARS-CoV-2 lung disease could be a secondary interferonopathy with pulmonary alveolar proteinosis (PAP)-like features and sometimes thrombotic microangiopathy. The clinical settings describes in SARS-CoV-2 infection, have their copy in different well known autoinflammatory syndromes. In this scene, we hypothesize that a targeted therapy against this innate inflammatory mechanism without deleterious effect in an infectious scenario would be the best option. An interesting therapeutic approach for the early stages of COVID-19-associated systemic and pulmonary disease would be specific IFN- $\gamma$  blockage. Emapalumab, a monoclonal anti-IFN $\gamma$  antibody, approved for the treatment of primary Hemophagocytic Lymphohistiocytosis (HLH) in children, has proven a powerful, fast, short and safe effect, and merit its consideration as a therapeutic approach in the early stages of COVID-19. In our opinion, a clinical trial to demonstrate this hypothesis and establish patient inclusion criteria, as well as treatment timing and duration, is justified.

## Opinion

Among patients with SARS-CoV-2 infection (COVID-19), 1-2% of patients develop a devastating acute systemic inflammatory picture with predominantly pulmonary expression. Several immune pathogenic portraits have been described and need wise consideration for targeted and non-deleterious therapy. Heterogeneous cytokines patterns, partially known molecular mechanism and, surely, different genetic background are likely to define the clinical setting beyond the age of the patients. Some SARS-CoV-2 patients show hyperimmune activation, including anomalous expression of interferon (IFN)-stimulated genes as it was seen in MERS and SARS-CoV patients. Elevated secretion of the cytokine IFN- $\gamma$ -induced protein-10, IFN- $\gamma$ , tumor necrosis factor- $\alpha$ , and IL-17, all of which are closely associated with virally mediated acute lung injury has been demonstrated [1].

The angiotensin-converting enzyme 2 (ACE2), whose principal role seems to be the degradation of angiotensin II, has been demonstrated to be used by SARS-CoV-2, as well as other coronaviruses, to enter the cells [2]. ACE2 is widely expressed in pulmonary alveolar epithelial cells, in endothelial vascular tissues, absorptive enterocytes and cardiac pericytes. These alveolar type II (AT2) cells are particularly prone to viral infection [3]. Some experimental studies have shown that ACE2-knock-out mice are not infected by these viruses [4]. Recent research has stated that SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial

cells [5]. This is the reason why COVID-19 is a systemic but predominantly pulmonary disease.

The production of the type I interferons (IFNs) IFN- $\alpha$  and IFN- $\beta$  is one of the most critical early events in the induction of an antiviral innate immune response. Type I IFN is induced during viral infection to activate the transcription of a number of IFN-stimulated genes (ISGs) that establish an antiviral state to limit the spread of the virus. TMEM173 gene encodes the protein STING (stimulator of interferon genes), a key player in host defense against pathogens. Human population is highly heterogeneous for the TMEM173. Polymorphisms in the human TMEM173 gene have been reported to result in a gain-of-function phenotype and are likely to contribute to severe inflammatory disorders. Also, Two possible loss-of-function alleles have been described: HAQ and H232. The

**\*Corresponding author:** Julián Fernández-Martín, MD, PhD, Department of Internal Medicine, Hospital Álvaro Cunqueiro, Estrada Clara Campoamor 341, 36213-Vigo-Pontevedra, Spain

**Received:** May 18, 2020

**Accepted:** June 13, 2020

**Published online:** June 15, 2020

**Citation:** Fernández-Martín J, Pérez-Álvarez R, Lamas-Barreiro JM (2020) COVID-19: An Acute Secondary Interferonopathy? The Mirror of Autoinflammatory Syndromes. Arch Immunol 2(1):18-21

HAQ/HAQ, H232/HAQ, and H232/H232 genotypes account for ~30% of East Asians and ~10% of Europeans.

Coronaviruses have STING evasion. The precise mechanism of STING antagonism remains to be clarified. It will also be important to define the contribution STING antagonism makes to the pathogenic potential of coronaviruses. The conservation of STING evasion among coronaviruses, and the role STING might play in restricting coronavirus host-switching are also exciting research avenues, especially given the emergence of three highly pathogenic coronaviruses in just over a decade [6].

The most common laboratory abnormalities in COVID-19 are a decreased level of neutrophils and lymphocytes, elevated C-reactive protein, fibrinogen, D-dimer, erythrocyte sedimentation rate and lactate dehydrogenase and decreased cytotoxic CD8+ T lymphocyte count [7]. Complement activity and ADAMS-13 have not been systematically studied. Severe patients have high levels of ferritin, but not as high as in the Hemophagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS) range. The cytokine circulating patterns are not clear until now and probably, the pathogenic tracks, are genetically dependent. Acute severe myocarditis (except for slight increase of blood levels of high-sensitive troponin-I cardiac biomarker), severe hepatic dysfunction, thrombotic microangiopathy, hemophagocytosis, neurological affection or other problems typical of MAS/HLH, are not usually present, except in isolated cases or critical patients. "Cytokine storm" is a central feature of HLH/MAS with a particular important role for IL-18 and interferon-gamma (IFN $\gamma$ ). While IFN $\gamma$  is difficult to measure, CXCL9 (IFN $\gamma$  inducible cytokine), soluble-IL-2 Receptor and IL-18 are available for clinical testing. The concept of a true and canonical systemic cytokine storm syndrome with HLH/MAS criteria and high H-score is not a frequent reality, although, it has been described and demonstrated in SARS-CoV-2 patients [8].

Despite the large number of patients worldwide with COVID-19, there is currently a shortage of pathological data from autopsy or biopsy. It being an acute process, the severity of the clinical situation of the patients, the high contagiousness and the frequent need for invasive mechanical ventilation, make a histological approach very risky and difficult.

In two patients with SARS-CoV-2, pathologic examinations of the lungs of both patients exhibited edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells. Hyaline membranes were present but not prominent. In both patients, a biopsy was done for lung cancer without knowledge of a SARS-CoV-2 infection and interestingly in preliminary stages of the disease [9]. The pathologic pattern was a typical for classic ARDS.

In a case report with postmortem lung biopsies, histological examination showed bilateral diffuse alveolar damage with cellular fibro-myxoid exudates, evident desquamation of pneumocytes and scarce hyaline membrane formation. The left lung tissue in this case, displayed pulmonary edema with hyaline membrane formation. Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were

seen in both lungs. Multinucleated syncytial cells with typically enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm and prominent nuclei were identified in the interalveolar spaces, showing viral cytopathic-like changes. No intranuclear or intracytoplasmic viral inclusions were identified [10].

Interestingly, even recognizing the limited number of these histological samples, the description resembles in some aspects, the findings described in the primary and secondary pulmonary alveolar proteinosis (PAP) [10,11]. Clear dysfunction of alveolar surfactant may be the first step in lung damage.

In five individuals with severe COVID-19, Magro C [12]. Documented that at least some SARS-CoV-2-infected patients who become critically ill suffer a generalized thrombotic microvascular injury. Such pathology involves at least the lung and skin, and appears mediated by intense complement activation. Specifically, they found striking septal capillary injury accompanied by extensive deposits of the terminal complement complex C5b-9 as well as C4d and MASP2 in the lungs of two cases examined. A similar pattern of pauci-inflammatory complement mediated microthrombotic disease in the skin of three cases with livedo reticularis and purpuric lesions, with C5b-9 and C4d deposition in samples taken from both cutaneous lesions and normal-appearing skin. These histologic findings are consistent with emerging observations suggesting that COVID-19 has clinical features distinct from typical ARDS. The pathology in all these cases might therefore be expected to differ from the diffuse alveolar damage and hyaline membrane formation which are hallmarks of typical ARDS. [13], the pulmonary abnormalities in other COVID-19 patients appear largely restricted to the alveolar capillaries with clear thrombotic microvascular injury and few signs of viral cytopathic or fibroproliferative changes. This pathologic pattern, atypical for classic ARDS, is accompanied by extensive deposition of alternative pathway and lectin pathway of complement components within the lung septal microvasculature. With such extensive complement involvement, membrane attack complex mediated microvascular endothelial cell injury and subsequent activation of the clotting pathway, leading to fibrin deposition, might be anticipated. It is also consistent with the very high d-dimer levels found in the cases of COVID-19 in which it was assessed.

Blocking C5a with a specific antibody against the C5a receptor (C5aR) reduces lung damage, due to a reduced alveolar macrophage infiltration and interferon (IFN)-gamma receptor expression, accompanied by a decreased viral replication. Complement is a known IFN $\gamma$  activator [12].

Both, monogenic and undifferentiated autoinflammatory syndromes, have served as valuable models for understanding the molecular mechanisms of the innate immune response. Three clinical entities have been described in this group of diseases with severe systemic and pulmonary involvement. In the recent paper of De Jesus, et al. [14], they describe undifferentiated systemic autoinflammatory diseases (USAID) with chronic interferon (IFN) signaling and cytokines regulation. In this study, eight patients with PAP and MAS were identified.

Moderate interferon signature elevation and highly elevated serum IL-18 distinguished this group of patients. Remarkably, high expression of IL-18 and IFN $\gamma$  were also identified in the bronchoalveolar lavage of patients with systemic juvenile idiopathic arthritis and adult onset still's disease lung damage [15].

SAVI is considered part of a growing group of Mendelian disorders defined "interferonopathies", characterized by severe uncontrolled activation of interferon and downstream genes. Patients with SAVI have severe neonatal-onset small vessel vasculitis leading to diffuse microangiopathic thrombosis, vessel occlusion, and even risk of gangrene. Some SAVI patients may present chronic interstitial lung disease. Mutations in the human TMEM173 gene cause this life-threatening auto-inflammatory disease (STING-associated vasculopathy with onset in infancy). Transbronchial lung biopsy (TBLB) was performed in one SAVI patient revealing thickened vascular walls with infiltrations of inflammatory cells and proliferation of vascular endothelial cells associated with some small vessel occlusion, which revealed the presence of pulmonary vasculitis which can be severe and lethal. In fact, the STING protein is expressed not exclusively in the vascular endothelial cells, but also in AT2 pneumocytes and in bronchial epithelium and alveolar macrophages, explaining the specific lung pathology: STING-induced dysfunction results in a vaso-occlusive process with activation of both local macrophages and pneumocytes [16].

SAVI is unique because it is the only known type I Interferonopathy with pulmonary involvement. In fact, all three reported fatalities from SAVI patients were due to the pulmonary complications. The activation of STING in the mouse lung by intranasal administration of CDNs, induced lung production of IFN $\gamma$  and IFN $\lambda$  but not IFN $\beta$ . Interestingly, IFN $\gamma$ +CD4+ T cells and serum IFN $\gamma$  were markedly increased in a recent SAVI patient. Notably, serum IL-18, a known IFN $\gamma$  inducer, was also elevated in several SAVI patients. Whether the increased IFN $\gamma$  production contributes to the lung symptoms in SAVI patients and in viral RNA infectious diseases is worth further investigation. There are clear coincidences between SAVI patients, Still's pulmonary disease, undifferentiated autoinflammatory disease with pulmonary involvement and SARS-CoV-2 severe disease. Interferon is the common link of all these processes [16].

The increase of IL-18-dependent-IFN during an infection may provide further potential mechanisms by which IL-18 confers MAS susceptibility. The presence of PAP suggests alveolar macrophage dysfunction in clearing surfactant from the alveoli. Whether IL-18 or IFN $\gamma$  blockage and/or treatments aimed at increasing surfactant phagocytosis/processing by alveolar macrophages are viable treatment strategies, needs further exploration. Probably, whole exome sequencing and genetic analysis, in the future, will open the light about the susceptibility and may identify persons and diseases with available targeted treatments.

Patients with severe and fatal cases of COVID-19 may have increased susceptibility through different genetic status. A common trigger, a pandemic, and millions of cases, has

been a tragic experiment to understand in times of precision medicine and targeted therapies, the different faces of the disease, clearly conditioned probably, by genetic and epigenetic variants.

Currently, the therapeutic approach to SARS-CoV-2 infection is purely empirical. Today, there is no antiviral specific treatment. Surprisingly and without definitive scientific evidence, high dose corticosteroids, hydroxychloroquine, beta-interferon, anakinra, eculizumab and tocilizumab are, in monotherapy or in combination, associated with different antivirals and antibiotics. Trials with are in development. It remains to be defined whether this logical and desperate attempt to treat is positive or even deleterious. In times of personalized medicine, perhaps, and in parallel with the auto-inflammatory syndromes with lung involvement and thrombotic microangiopathic and PAP-like histological pictures, a therapeutic approach in the early stages of COVID-19 lung involvement with specific interferon blockade should be considered.

COVID-19 is an acute "one shot" viral disease with an unpredictable evolution. In severe patients, an early fast, short and safety therapeutic intervention is necessary before the development of irreversible lung damage. Clinical data, analytical findings and the few pathological references aim to consider SARS-CoV-2 systemic and lung disease as a secondary interferonopathy. A targeted therapy against the inflammatory mechanism without deleterious effect in an infectious scenario would be the best option. An interesting therapeutic approach for the early stages of pulmonary involvement of COVID-19 would be the specific IFN- $\gamma$  blockage.

JAK  $\frac{1}{2}$  inhibition with Baricitinib has been proposed as an option in IL-18 and Interferon mediated diseases. Richardson P, et al. [17] suggest using that drug with an appropriate patient selection in patients with SARS-CoV-2 pneumonia. Its oral administration and erratic absorption in severe and ventilated patients is an important limitation. Gastrointestinal symptoms are frequent in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients. Among the 95 patients of a clinical study in China, 58 cases exhibited gastrointestinal (GI) symptoms of which 11 (11.6%) occurred on admission and 47 (49.5%) developed during hospitalization. Diarrhea (24.2%), anorexia (17.9%) and nausea (17.9%) were the main symptoms with five (5.3%), five (5.3%) and three (3.2%) cases occurred on the illness onset, respectively [18].

Emapalumab, a monoclonal antibody anti-IFN $\gamma$ , is the first cytokine-targeting therapy approved specifically for the treatment of HLH. This treatment has been used in children with refractory and primary HLH and resulted in a high overall response rate [19], even with concurrent infections [20]. Its powerful, fast, short and safe effect could be an added benefit to avoid a deep and prolonged immunosuppression in an acute viral disease. Primary HLH is a predominantly disease of children. The vast majority of HLH in adults is secondary HLH. It remains to be seen how efficacious this treatment will be in adult patients with HLH, for whom it was approved, despite the lack of clinical trial data.

In conclusion, an interesting therapeutic approach for the

early stages of pulmonary involvement of COVID-19 would be the IFN- $\gamma$  blockage. A clinical trial to demonstrate this hypothesis and to determine the type of patient, the time of treatment and its duration is justified.

## References

1. Rudragouda Channappanavar, Stanley Perlman (2017) Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 39: 529-539.
2. Carly GK Ziegler, Samuel J Allon, Sarah K Nyquist, et al. (2020) SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 181: 1016-1035.
3. Lamas-Barreiro JM, Alonso-Suárez M, Fernández-Martín J, et al. (2020) Angiotensin II suppression in SARS-CoV-2 infection: A therapeutic approach. *Nefrologia*.
4. Imai Y, Kuba K, Penninger JM (2008) The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. *Exp Physiol* 93: 543-548.
5. Zhao Y, Zhao Z, Wang Y, et al. (2020) Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *bioRxiv*.
6. Maringer K, Fernandez-Sesma A (2014) Message in a bottle: Lessons learned from antagonism of STING signalling during RNA virus infection. *Cytokine & Growth Factor Reviews* 25: 669-679.
7. Liu Y, Yang Y, Zhang C, et al. (2020) Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 63: 364-374.
8. Halyabar O, Chang MH, Schoettler ML, et al. (2019) Calm in the midst of cytokine storm: A collaborative approach to the diagnosis and treatment of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. *Pediatr Rheumatol* 17: 7.
9. Tian S, Hu W, Niu L, et al. (2020) Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol* 15: 700-704.
10. Khan A, Agarwal R (2011) Pulmonary alveolar proteinosis. *Respir Care* 56: 1016-1028.
11. Albogami SM, Touman AA (2019) Viral pneumonia and pulmonary alveolar proteinosis: The cause and the effect, case report. *AME Case Reports* 3: 41.
12. Cynthia Magro, J Justin Mulvey, David Berlin, et al. (2020) Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Translational Research* 15.
13. Xu Z, Shi L, Wang Y, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 8: 420-422.
14. De Jesus AA, Hou Y, Brooks S, et al. (2020) Distinct interferon signatures and cytokine patterns define additional systemic autoinflammatory diseases. *J Clin Invest* 130: 1669-1682.
15. Schulert GS, Yasin S, Carey B, et al. (2019) Systemic Juvenile Idiopathic Arthritis-Associated Lung Disease: Characterization and Risk Factors. *Arthritis Rheumatol* 71: 1943-1954.
16. Yao Cao, Li-ping Jiang (2019) The Challenge of Diagnosing SAVI: Case Studies. *Pediatric Allergy, Immunology, and Pulmonology* 32: 167-172.
17. Richardson P, Griffin I, Tucker C, et al. (2020) Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 395: e30-e31.
18. Lin L, Jiang X, Zhang Z, et al. (2020) Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 69: 997-1001.
19. Vallurupalli M, Berliner N (2019) Emapalumab for the treatment of relapsed/refractory hemophagocytic lymphohistiocytosis. *Blood* 134: 1783-1786.
20. Lounder DT, Bin Q, De Min C, et al. (2019) Treatment of refractory hemophagocytic lymphohistiocytosis with emapalumab despite severe concurrent infections. *Blood Adv* 3: 47-50.

DOI: 10.36959/885/368