

# Dexamethasone, pro-resolving lipids and resolution of inflammation in COVID-19

Evangelos Andreacos<sup>1</sup>, Maria Papadaki<sup>1</sup>, and Charles Nicholas Serhan<sup>2</sup>

<sup>1</sup>Biomedical Research Foundation, Academy of Athens

<sup>2</sup>Harvard Medical School

July 16, 2020

## EDITORIAL

Coronavirus disease-19 (COVID-19) is a new disease caused by SARS-CoV2. Since the beginning of 2020, it has become one of the main challenges of our times, causing a high incidence of severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure and death<sup>1</sup>. At the root of COVID-19 lies the sudden development of ‘cytokine storms’, hyper-inflammatory responses involving the release of pro-inflammatory cytokines (e.g., TNF- $\alpha$ , IL-6, IL-1, IL-8, and MCP-1) that impair the gas exchange function of the lung and lead in select patients, mostly with underlying comorbidities, to multiorgan failure and death<sup>1,2</sup>. Additional complications triggered by ‘cytokine storms’ include endothelial dysfunction and hypercoagulation, increasing the risk of thromboembolytic events, and life-threatening cardiovascular complications. Anti-inflammatory therapies are thus being considered for alleviating the damaging side effects of hyper-inflammation with many trials including anti-cytokine biologicals, disease-modifying antirheumatic drugs (DMARDs) and corticosteroids being ongoing<sup>3</sup>. Surprisingly, among them dexamethasone has taken center stage as initial results from the *RECOVERY* trial, a large multicenter randomized open-label trial for hospitalized patients run in the United Kingdom, revealed notable efficacy in the treatment of critically ill COVID-19 patients<sup>4</sup>.

Dexamethasone is one of the oldest synthetic glucocorticoid agonists synthesized in 1957 and introduced into the clinic in 1961. When administered at 6 mg daily, either orally or intravenously for 10 days, dexamethasone was shown in the *RECOVERY* trial to improve survival rates of hospitalized patients with severe COVID-19 receiving oxygen or being on mechanical ventilation by a remarkable 30%<sup>4</sup>. Benefit was restricted to patients requiring respiratory support whereas in milder cases this was not clear. This notable efficacy of dexamethasone treatment goes against the current view of corticosteroid use in respiratory viral infections which remains contradictory. Although corticosteroids improve ventilator weaning and can lower the intensity of the host response to the virus, tempering the ‘cytokine storm’ and limiting immunopathology, they can also reduce viral clearance and lead to more severe disease. Understanding therefore how dexamethasone mediates its effects is of paramount importance.

Dexamethasone, as other corticosteroids, is held to mediate its anti-inflammatory and immunosuppressive effects via the glucocorticoid receptor. Upon ligand binding, the receptor-corticosteroid molecule complex moves into the cell nucleus, where it dimerizes and binds to glucocorticoid response elements (GRE), acting as transcriptional repressor or transactivator of diverse sets of genes. This results in the inhibition of inflammatory cell activity, including neutrophils, macrophages and lymphocytes, and the suppression of pro-inflammatory cytokines such as TNF and interleukins and other genes such as cyclooxygenase-2 and inducible nitric oxide synthase<sup>5</sup>. However, we have recently uncovered that dexamethasone can also induce the D-series proresolving lipid mediator pathway leading to the production of 17-HDHA and the protectins D1 and DX<sup>6</sup>. These are potent major players of the molecular machinery driving the resolution of inflammation, i.e. the proper regulated termination of pro-inflammatory responses involving the catabolism of pro-inflammatory

mediators, the removal of inflammatory cells and the restoration of the tissue in a timely and highly coordinated manner<sup>7</sup>. Although resolution of inflammation has long been considered to occur spontaneously as a result of the waning of pro-inflammatory responses, this is now known to be an ordered and highly regulated process involving the timely production of enzymatically oxygenated lipid-derived mediators such as protectins, D-series resolvins and maresins derived from the omega-3 fatty acid docosahexaenoic acid (DHA), E-series resolvins derived from eicosapentaenoic acid (EPA), and lipoxins biosynthesized from omega-6 fatty acids following eicosanoid class switching<sup>7</sup>. Interestingly, certain lipid mediators have been shown to exert additional non-conventional functions; resolvin D4 can attenuate pathologic thrombosis, reduce NETosis and promote clot removal<sup>8</sup> which is now recognized as a key pathology of COVID-19 infection, while resolvin E4 (RvE4) stimulates efferocytosis of senescent erythrocytes in hemorrhagic exudates especially under hypoxic conditions that characterize COVID-19<sup>9</sup>. Moreover, corticosteroids have been reported to reduce fibrinogen and procoagulant factors under pro-inflammatory conditions and increase anticoagulant factors<sup>10</sup>.

The ability of viral infections to induce proresolving lipids has been reported earlier. Toll-like receptor 7 (TLR7), a major pattern recognition receptor of viral RNA, activates PD1 and PDX production<sup>11</sup>. Moreover, influenza virus infection has been demonstrated to drive proresolving lipid mediator networks including the production of PD1 which limits influenza pathogenicity by directly interacting with the RNA replication machinery to inhibit viral RNA nuclear export<sup>12,13</sup>. Notably, in particularly virulent strains of influenza virus such as the H5N1 avian strain, PD1 formation is not sufficiently upregulated, leading to more efficient viral replication and host demise<sup>12</sup>. It is therefore plausible that the efficacy of dexamethasone in COVID-19 is due at least in part to its ability to induce proresolving lipid mediators that possess multiple anti-inflammatory and proresolving actions tempering down inflammation and promoting its resolution, preventing coagulation and enhancing viral and bacterial clearance (Figure 1) yet are not immunosuppressive. Whether other corticosteroids beyond dexamethasone can also mediate such effects, and to what extent, is not known. Whether inhalable corticosteroids, such as those given to asthmatic patients, can also induce proresolving lipid mediator networks locally and thus prevent the development of severe SARS-CoV-2 infection remains to be determined. There is evidence that asthmatic patients exhibit reduced incidence of severe and/or critical COVID-19<sup>14</sup>.

Recently, COVID-19 patients showed increased association of serum arachidonate-derived proinflammatory lipid mediators, e.g. prostaglandins, in severe COVID-19 infections while some pro-resolving mediators such as resolvin E3 were up-regulated in the moderate COVID-19 group suggesting that an imbalance in lipid mediators with a swift toward pro-inflammatory mediators in severe disease may contribute to COVID-19 disease severity<sup>15</sup>. Although the involvement of proresolving lipid mediator pathways in COVID-19 is an attractive hypothesis, further evidence from human trials is needed as there are no studies at present reporting the induction or modulation of such networks in the context of the various disease stages and treatments. It is thus of uttermost priority to investigate proresolving lipid mediators in COVID-19, in a temporal and longitudinal manner, as modulating these networks either through drug treatment or direct administration of resolvin and protectins agonists has the potential to affect this highly lethal and devastating disease in a way other approaches cannot. Such studies are therefore eagerly awaited.

## Figures

**Figure 1. Hypothetical model of dexamethasone mode of action involving inhibition of the cytokine storm and induction of proresolving lipids such as Protectin D1 (PD1) and Resolvin D4.** SARS-CoV2 infection induces hyperinflammation characterized by a ‘cytokine storm’ involving TNF, IL-1, IL-6, IL-8 and IP-10 production and release of eicosanoids. SARS-CoV2 infection also induces proresolving mediators including protectins, resolvins and maresins as an effort to counter-balance the system. These act to reduce inflammation and promote its resolution but are also help resolve coagulation and block viral replication. Strengthening this response through the temporal administration of dexamethasone which triggers in addition to its conventional anti-inflammatory effects the D-series protectins results in notable benefit in patients.

## Acknowledgements

EA is supported by research grants from the European Commission (IMMUNAID, No 779295 and CURE, No. 767015) and the Hellenic Foundation for Research and Innovation (INTERFLU, No 1574). CNS contributions are supported by the NIH grant P01GM095467.

### Conflict of interest

The authors declare no conflict of interest.

### References

- 1 Guan, W. J. *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* **382** , 1708-1720, doi:10.1056/NEJMoa2002032 (2020).
- 2 Wu, C. *et al.* Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* , doi:10.1001/jamainternmed.2020.09942763184 [pii] (2020).
- 3 Sanders, J. M., Monogue, M. L., Jodlowski, T. Z. & Cutrell, J. B. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* , doi:10.1001/jama.2020.60192764727 [pii] (2020).
- 4 Horby, P. *et al.* Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. *medRxiv* , 2020.2006.2022.20137273, doi:10.1101/2020.06.22.20137273 (2020).
- 5 Rhen, T. & Cidlowski, J. A. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med* **353** , 1711-1723, doi:353/16/1711 [pii]10.1056/NEJMra050541 (2005).
- 6 Pyrillou, K., Chairakaki, A. D., Tamvakopoulos, C. & Andreakos, E. Dexamethasone induces omega3-derived immunoresolvents driving resolution of allergic airway inflammation. *J Allergy Clin Immunol* **142** , 691-695 e694, doi:S0091-6749(18)30612-2 [pii]10.1016/j.jaci.2018.04.004 (2018).
- 7 Serhan, C. N. Pro-resolving lipid mediators are leads for resolution physiology. *Nature***510** , 92-101, doi:10.1038/nature13479nature13479 [pii] (2014).
- 8 Cherpokova, D. *et al.* Resolvin D4 attenuates the severity of pathological thrombosis in mice. *Blood* **134** , 1458-1468, doi:10.1182/blood.2018886317blood.2018886317 [pii] (2019).
- 9 Norris, P. C., Libreros, S. & Serhan, C. N. Resolution metabolomes activated by hypoxic environment. *Sci Adv* **5** , eaax4895, doi:10.1126/sciadv.aax4895aax4895 [pii] (2019).
- 10 van Zaane, B. *et al.* Systematic review on the effect of glucocorticoid use on procoagulant, anti-coagulant and fibrinolytic factors. *J Thromb Haemost***8** , 2483-2493, doi:10.1111/j.1538-7836.2010.04034.xJTH4034 [pii] (2010).
- 11 Koltsida, O. *et al.* Toll-like receptor 7 stimulates production of specialized pro-resolving lipid mediators and promotes resolution of airway inflammation. *EMBO Mol Med* **5** , 762-775, doi:10.1002/emmm.201201891 (2013).
- 12 Morita, M. *et al.* The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. *Cell* **153** , 112-125, doi:10.1016/j.cell.2013.02.027S0092-8674(13)00216-X [pii] (2013).
- 13 Tam, V. C. *et al.* Lipidomic profiling of influenza infection identifies mediators that induce and resolve inflammation. *Cell* **154** , 213-227, doi:10.1016/j.cell.2013.05.052S0092-8674(13)00695-8 [pii] (2013).
- 14 Avdeev, S. *et al.* Low prevalence of bronchial asthma and chronic obstructive lung disease among intensive care unit patients with COVID-19. *Allergy* , doi:10.1111/all.14420 (2020).
- 15 Schwarz, B. *et al.* Severe SARS-CoV-2 infection in humans is defined by a shift in the serum lipidome resulting in dysregulation of eicosanoid immune mediators. *medRxiv* , doi:10.1101/2020.07.09.20149849 (2020).

