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Inositol and pulmonary function. Could myo-inositol treatment downregulate inflammation and cytokine release syndrome in SARS-CoV-2?

M. BIZZARRI[1,2], A.S. LAGANÀ[3], D. ARAGONA[4], V. UNFER[2]

[1]Department of Experimental Medicine, Sapienza University, Rome, Italy
[2]Systems Biology Group Lab, Rome, Italy; website: www.sbglab.org
[3]Department of Obstetrics and Gynecology, Center of Excellence in Minimally Invasive Gynecology (COEMIG) "Filippo Del Ponte" Hospital, University of Insubria, Varese, Italy
[4]AUSL Latina, "Santa Maria Goretti" Hospital, Latina, Italy

Abstract. **The outbreak of Sars-CoV-2 (COVID-19) poses serious challenges to people's health worldwide. The management of the disease is mostly supportive, and respiratory failure from acute respiratory distress syndrome is the leading cause of death in a significant proportion of affected patients. Preliminary data point out that dramatic increase in IL-6 and subsequent cytokine release syndrome may account for the development of fatal interstitial pneumonia. Inhibition of IL-6 by blocking its specific receptor with monoclonal antibodies has been advocated as a promising attempt. Here we assess the potential utility of myo-Inositol, a polyol already in use for treating the newborn Respiratory Distress Syndrome, in downregulating the inflammatory response upon Sars-CoV-2 infection. Myo-Inositol proved to reduce IL-6 levels in a number of conditions and to mitigate the inflammatory cascade, while being devoid of any significant side effects. It is tempting to speculate that inositol could be beneficial in managing the most dreadful effects of Sars-CoV-2 infection.**

Key Words:
Sars-CoV-2, COVID-19, Myo-Inositol, Acute Respiratory Distress Syndrome, Interleukin-6 (IL-6).

Sars-CoV-2 (Covid-19) Epidemics

A coronavirus-based disease – Sars-CoV-2, previously known as COVID-19 - is currently spreading worldwide[1]. Current management of COVID-19 is mostly supportive, and respiratory failure from acute respiratory distress syndrome is the leading cause of death. Despite corticosteroids should be avoided as they might worsen lung damage (as demonstrated by previous pandemics), down-regulation of immune function is deemed beneficial given that patients with severe COVID-19 might display a cytokine storm syndrome. Thereby, new treatment options are urgently warranted.

Inositol and Pulmonary Function

Inositol and Respiratory Distress Syndrome in the newborn. In 1955, Pattle et al[2] described the pulmonary surfactant (PS) and provided the first evidence about the involvement of PS in several lung diseases. Pulmonary surfactant is a surface-active lipoprotein complex (phospho-lipoprotein) formed by type II alveolar cells[3,4]. Secondary alveolarization, begins at about 32 weeks' gestation. During this phase, alveoli form and mature, and alveolar walls thin. All cell types proliferate during this phase, including type II pneumocytes. The overall result is a maturing lung with a larger surface area and a minimal diffusion distance for gas exchange[2]. Abnormalities in surfactant composition and/or reduced surfactant synthesis have been described in Respiratory Distress Syndrome[5] (RDS, formerly known as hyaline membrane disease) in the infants, as well as in many similar illnesses[6]. Indeed, the absence or the inadequacy of surfactant in the liquid film lining of alveoli cause an increase in surface tension and alveolar collapse[7]. Furthermore, RDS may lead to very severe forms of Chronic Lung Disease (CLD)[8], even if after the introduction of RDS therapy those clinical pictures have been less frequently recorded. Actually, current CLD form comprises incomplete growth and development of alveoli and vasculature, sustained inflammatory cell activation, akin to that of chronic

Corresponding Author: Mariano Bizzarri, MD, Ph.D; e-mail: mariano.bizzarri@uniroma1.it

obstructive disease. A prominent feature of CLD is a persistent/recurrent inflammatory reaction, due to several factors: hyperoxia, baro/volu-traumas, toxin stimulation, intrauterine infections[9]. Accordingly, anti-inflammatory drugs proved to ameliorate clinical symptoms, even if glucocorticoid should be avoided. Researchers have recently focused interest on the use of myo-inositol (myo-Ins) supplementation in preterm infants for the prevention of bronchopulmonary disease (BPD) and retinopathy of prematurity (ROP)[10-12]. Myo-Ins is a naturally occurring polyol, widely represented in foods and actively synthesized by living organisms, that is involved in a number of critical physiological processes[13]. In the lung, myo-Ins promotes maturation of the surfactant phospholipids, phosphatidylcholine and phosphatidyl-inositol. Namely, the synthesis of phosphatidylinositol in type II pneumocytes appears to be dependent on extracellular inositol concentrations[14,15]. Compositional changes in fetal rat lung surfactant correlate with changes in plasma inositol levels, and supplementation restores normal phospholipid levels in the deprived rat pup[16,17].

In human infants with RDS, a premature drop in serum inositol levels predicts a more severe course[18]. Inositol supplementation increases the saturated phosphatidylcholine/sphingomyelin ratio in surfactant in newborns, and produces a rise in serum inositol concentration. In humans, free inositol levels in sera from preterm neonates are 2-20 times higher than maternal or adult sera[19,20]. Human milk has a high concentration of inositol, with preterm milk being the richest source, and studies in newborns suggest an endogenous synthesis of inositol during fetal life. Infants who are breast fed have higher serum inositol levels compared to those that are not at 1-2 weeks of life[21,22]. These facts suggest a critical role for inositol in fetal and early neonatal life. Several studies have been published assessing serum inositol levels in the preterm human infant[23,24], as well as the effects of inositol supplementation. However, only few published RCTs of inositol supplementation have been subjected to systematic review[25]. Yet, while the number of studies available for analysis was small, the quality of the reports was considered appropriate, as recently stated by a Cochrane study[26]. A statistically significant reduction in death or BPD in infants with inositol supplementation was indeed demonstrated, and a striking reduction was found in ROP stage 4 or in that needing treatment. When a secondary analysis was carried out, a significant reduction was observed in ROP (any stage) as well[26]. A further survey released in 2012[27] recorded five randomized clinical trials, reaching similar conclusions: myo-Ins supplementation results in statistically significant and clinically important reductions in short-term adverse neonatal outcomes, decreases the incidence of broncho-pulmonary dysplasia and significantly reduces neonatal death.

The effectiveness of myo-Ins in reducing the severity of RDS is consistent with experimental data indicating that it serves as a substrate to enhance the synthesis and the secretion of surfactant phospholipid in immature lung tissue[28]. It is unclear whether the decrease in RDS severity in newborns treated with myo-Ins was due to the surfactant increase – as documented by the significant increase in lecithin:sphingomyelin ratio during the first days of life – or to the effect on other lung structural and molecular components as well. Those data prompted clinicians to investigate the usefulness of myo-Ins in the combined treatment of other diseases of the upper and lower respiratory system (acute sinusitis, chronic obstructive bronchopneumopathy, bronchiolitis and eventually lung cancer).

Inositol and Lung Cancer

Dietary inositol has been shown to inhibit lung tumorigenesis in female A/J mice exposed to the carcinogen benzo(α)-pyrene or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in a number of studies[29-33]. With doses as low as 0.3% added to the diet, myo-Ins inhibited pulmonary tumor formation by 53% when given continuously, starting one week before benzo(α)-pyrene administration[34]. Moreover, combination of myo-Ins with dexamethasone was the only chemopreventive regimen that attenuated the weak carcinogenicity of unfractionated environmental carcinogenic compounds[35]. Myo-Ins was also effective in the post-initiation phase and when given for short periods before, during, and immediately post carcinogen exposure[36]. In humans, myo-Ins in a daily dose of 18 g *per os* showed to be safe and well tolerated, meanwhile inducing a significant regression of individual pulmonary dysplastic lesions (91% in the myo-Ins group versus 48% in the placebo group)[37]. Myo-Ins plays a relevant set of pleiotropic effects on several different pathways that can collectively exert many of anticancer activities (inhibition of cell proliferation, increased apoptosis, modulation

of cytoskeleton architecture and so forth)38,39. As PI3K activation represents a critical and early step in lung carcinogenesis, its inhibition is likely to be a key factor in lung cancer chemoprevention. Indeed, a significant increase in a genomic signature of phosphatidylinositol 3-kinase (PI3K) pathway activation in cells from the bronchial airway of both smokers with lung cancer and smokers with dysplastic lesions has been recorded, suggesting that PI3K is activated in the proximal airway before tumorigenesis. It is worth noting that PI3K activity decreases in the airway of high-risk smokers who had significant regression of dysplasia after treatment with the chemopreventive agent myo-Ins[40]. Moreover, following myo-Ins treatment, significant decreases in Akt and ERK phosphorylation were observed in dysplastic lung lesions ($p<0.05$) *in vivo*; *in vitro*, inositol decreased endogenous and tobacco carcinogen-induced activation of Akt and ERK in immortalized human bronchial epithelial cells, ultimately leading to decreased cell proliferation and to G1-S cell cycle arrest[41]. Besides the inhibitory effect upon "canonical" pathways, myo-Ins demonstrated to modulate a number of other relevant biochemical cascades. In a transgenic mouse oncogenic Kras model (CC-LR), myo-Ins significantly reduces cancer development while reducing oncogenic KrasG12D and downstream effectors, cRaf and p-ERK in the lungs of CC-LR mice. Given that CC-LR mice exhibited a substantially higher inflammatory cytokines (IL-6 and Leukaemia Inhibiting Factor, LIF), it was hypothesized that myo-Ins could interfere with the inflammatory pathway. As a result, it was showed that the activity of both IL-6 and LIF significantly decreases in lungs of CC-LR mice when they were fed with myo-inositol diet[42]. Additionally, those animals displayed a concomitant suppression of pStat3 activity.

Those data further confirm the differentiating activity exerted by myo-Ins and provide meaningful insights into new chemoprevention strategies[43]. All of these findings support the ongoing phase 2 multicenter study sponsored by the NCI Mayo Clinic Cancer Prevention Network[44].

IL-6 release and Acute Respiratory Distress Syndrome

Pathogenic human coronavirus infections, such as the current CoVid-19 (Sars-CoV-2), is associated with high mortality in a fraction (5-10%) of patients in which the virus triggers an interstitial pneumonia that quickly evolves into a severe respiratory distress syndrome (pneumonia associated respiratory syndrome, PARS)[45]. Even though the mechanisms that orchestrate PARS are still unknown, preliminary data suggest that a deregulated cytokine response (akin to the Cytokine Release Syndrome) plays a critical role, as already shown in previous corona-virus infections[46,47]. Indeed, it has been shown that CD4 T lymphocytes are rapidly activated to become pathogenic T helper-1 cells, subsequently unleashing a "cytokine storm" through increased expression of IL-6 and many other cytokines, thus promoting the recruitment of inflammatory CD14 and CD16 monocytes[48]. Indeed, lungs of Sars-CoV-2 patients are infiltrated by a large amount of inflammatory cells that disrupt the interstitium and alter the physiological cross-talk between cells and their microenvironment, thus hindering O_2 exchange[49]. Moreover, inflammatory cells and cytokines can enter the blood and play a relevant role in initiating a Multiple organ dysfunction syndrome[50]. It is remarkable that patients who develop PARS when infected by Sars-CoV-2 are mostly affected by a number of co-morbidities associated with persistent high levels of IL-6[51]: hypertension (73.8%)[52], cardiovascular diseases (52.1%)[53], cancer (19.5) and chronic renal failure (20.2)[54]. We hypothesize that Sars-CoV-2 infection can further exacerbate IL-6 release in these patients in which IL-6 levels are already very high, thus fostering a true cytokine storm[55].

IL-6 is a multifunctional cytokine that regulates humoral and cellular responses, playing a pivotal function in inflammation and tissue damage during infections and degenerative diseases (atherosclerosis, cancer). IL-6 acts through interaction with the receptor complex, IL-6Rb (also known as gp130), which transduces IL-6 effect into the cell. IL-6 levels are higher in patients affected by cardiovascular diseases[56], hypertension[57], in diabetes[58], as well as in other relevant diseases like cancer[59], deregulated inflammatory response[60], sepsis[61], and viral infections[62]. It is worth noting that patients with persistently elevated IL-6 levels demonstrate a worse in-hospital outcome following admission[63,64].

It is widely recognized that IL-6 can promote carcinogenesis, angiogenesis and metastasis in a number of experimental animal models[65]. Moreover, IL-6 mediated inflammatory pathway renders lung cancer cells resistant to cisplatin treatment[66], while higher systemic IL-6 levels are

associated with poor prognosis in non-small cell lung cancer[67].

New Therapeutic Perspectives in Counteracting IL-6 Storm Release

These preliminary data support the hypothesis of a causative role of IL-6 in driving the inflammatory response that leads to morbidity and mortality in patients with COVID-19 who develop acute respiratory distress syndrome. Therefore, it has been proposed that monoclonal antibodies targeting IL-6 or drugs able to downregulate IL-6 may be effective in blocking inflammatory storms, therefore representing a potential treatment for severe COVID 19 patients. Some promising, albeit unconfirmed, clinical results have shown that tocilizumab, a specific inhibitor of IL-6 receptor[68], can significantly improve oxygenation and clinical outcome of Sars-CoV-2 patients[69]. However, IL-6 has a role in both the innate and adaptive immune responses that protect the host from a variety of infections. Clinical studies of IL-6 inhibitors, specifically tocilizumab, revealed that their use is associated with an increased rate of both serious and opportunistic infections generally observed with other non-IL-6-directed biologic therapies[70].

High concentrations of inositol (or its derivatives) in surfactant preparations mitigate key inflammatory pathways in inflammatory lung disease[71]. Inositol and its metabolites also decrease pulmonary edema after lung injury[72]. In an animal model of Ovarian hyperstimulation syndrome (OHSS) – a condition that in some instances can be characterized by life-threatening events, like acute respiratory distress syndrome (ARDS), hypovolemia, ascites, edema, and thrombosis[73] – myo-Ins was able to counteract the main clinical features, while significantly reducing a number of inflammatory signatures, including Vascular permeability, VEGF and COX-2 expressions[74].

Moreover, inositol specifically down-regulates IL-6 levels[42], PI3K[75] (a key factor in the transduction of IL-6 signal), as well as many inflammatory parameters – like PGE and COX2[76] – downstream of PI3K activation in different diseases like cancer and polycystic Ovary Syndrome (PCOS). In this latter condition, myo-Ins supplementation significantly reduces pro-inflammatory cytokines like IL-6 and p-STAT3[77]. A general model has been proposed in which the chemo-protective effect of myo-Ins on lung functionality was directly linked to downregulation of IL-6 and modulation of the microenvironment immune response[78]. Again, it should be stressed that myo-Ins administration – both through intravenous route and by oral supplementation – is almost completely devoid of any significant adverse effect.

Overall, these findings suggest that IL-6 is a major target of myo-Ins and raise the possibility that Sars-CoV-2 patients with IL-6-driven inflammation may benefit from myo-Ins treatment.

Our laboratory already showed familiarity with the IL-6 release and the underlying mechanisms that regulate it. Specifically, we showed that IL-6, as well as IL-1b, are epigenetically upregulated by the hypomethylation of the gene promoter region in cell culture models and in human specimens from neurodegenerative disorders[79-81]. Unpublished preliminary results indicating that myo-Ins seems to exert epigenetic effects, suggest a possible mechanism of action in IL-6 regulation.

Overall, these findings indicate that IL-6 is a major target of myo-inositol and raise the possibility that Sars-CoV-2 patients with a high level of IL-6-driven inflammation may show benefit from treatment with myo-inositol.

Conflict of Interests

V.U. is an employee of Lo.Li.Pharma Srl. All other authors declare that they have no conflict of interests.

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