Indomethacin in covid-19, more than just NSAID

(An opinion article)

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As the drastic effects of SARS-CoV-2 was proven to be primarily triggered by inflammatory responses, Indomethacin could play a dual role in reversing these effects besides its reported antiviral activity. Previously, Indomethacin showed virucidal effects against **V**SV, **SARS-CoV-1**, **SARS-CoV-2** *in vitro* and **CCV** *in vivo* without inducing cellular toxicity [1-3]. The reported mechanism is thought to be due to the inhibition of the viral protein translation through the activation of **PKR** with subsequent phosphorylation of elF-2 alpha impacting viral replication. Preliminary reports stated that the SARS-CoV-2 NP-7 which is part of the viral replicase-transcriptase complex potentially binds to **PTGES-2** which could be also inhibited by Indomethacin [4].

Moreover, Indomethacin could bind and increase the expression of the immunomodulatory transcriptional factor **PPAR-γ** [5]. This may allow to tackle down the hyperactive immune system, and decrease the high pool of circulating cytokines during SARS-CoV-2 infection [6]. **PPAR-γ** decreases the production of the pro-inflammatory cytokines IL-6, IL-1B, TNF-α, IL-12 and controls macrophage functions while its deletion has resulted in a prominent increase in their activity combined with a decrease in the production of the anti-inflammatory cytokines such as IL-10 [7]. Extensive alveolar damage was the most remarkable manifestation observed in autopsies obtained from COVID-19 deceased patients [8]. Mall *et al*, demonstrated the efficacy of Indomethacin in the protection against Bleomycin-induced fibrosing alveolitis [9]. In context, **PPAR-γ** was reported to have a protective role against cytokines treated human lung epithelia through inhibition of **MCP-1** [10]. The same study elucidated that **PPAR-γ** is highly expressed in type-II alveolar cells as compared to type-I [10]. Interestingly, earlier studies showed that SARS-CoV-2 utilizes **ACE-2** as the entry point to infect cells which is predominantly expressed on type-II pneumocytes as well [11]. We speculate that the binding of Indomethacin to **PPAR-γ** expressed on type-II alveolar cells allows it to counteract the effects of the virus immunologically and anti-virally in a localized form.

Furthermore, Indomethacin could also help patients experiencing hypoxia secondary to the impaired gaseous exchange at alveolar cells recover quickly through the inhibition of **HIF-1α** [12]. **HIF-1α** is implicated in the recruitment of macrophages and lymphocytes to hypoxic regions further exacerbating inflammation [13, 14]. Previous studies showed that loss of **HIF-1α** in myeloid lineages impaired their functions in terms of migration, invasion and clustering through a metabolic pathway by decreasing the availability of ***ATP*** leading to a decline in the magnitude of inflammation and joint damage in RA [14]. In addition, aerosolized Indomethacin successfully helped patients with bronchoalveolar carcinoma having refractory bronchorrhea overcome dyspnea and regain normoxemia [15]. The same drug was shown to have a protective role against thrombi formation, a commonly reported problem with SARS-CoV-2 infection. In the study conducted by Short and colleagues, Indomethacin improved survival in rat models by **43%** compared to only **17%** in controls following *E.Coli* induced sepsis [16].

In line with clinical trials, the administration of Indomethacin **75 mg** for five days along with Remedisivir reduced the time to recover in severely affected COVID-19 patients [17]. The same authors pointed that Indomethacin is superior to Paracetamol in terms of symptomatic treatment that could be replaced whenever no contraindications or gestation are present [17]. In a prior study, Indomethacin showed benefits in patients with mild form of COVID-19 who are on immunosuppressive therapy following renal engrafting with minor side effects [18]. These results are consistent with the findings reported by Rothstein and colleagues in New York [19]. The current statement of WHO does not recommend against the use of NSAIDS during COVID-19, considering its promising outcomes, Indomethacin appears to be a good choice during COVID-19 setting while it also urges the need to incorporate it in controlled double-blinded clinical trials of larger sample sizes to officially validate its actions.

Abbreviations:

SARS-CoV-2: Severe Acute Respiratory Syndrome-Corona virus-2

VSV: Vesicular Stomatitis Virus

CCV: Canine Corona Virus

PKR: Protein Kinase R

elF-2 alpha: Eukaryotic Initiation Factor-2 alpha

NP-7: Non- structural Protein-7

PTGES-2: Prostaglandin E Synthase-2

PPAR-γ: Peroxisome Proliferator Activated Receptor-gamma

TNF-alpha: Tumor Necrosis Factor- alpha

MCP-1: Monocyte Chemoattractant Protein-1

ACE-2: Angiotensin Converting Enzyme-2

HIF-1α: Hypoxia-Inducible Factor-1 alpha

RA: Rheumatoid Arthritis

NSAIDS: Non-Steroidal Anti-inflammatory Drugs

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