NFκB inhbitor (SC75741) -Magic stick for COVID-19

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Abstract: The novel corona virus, previously dubbed 2019-nCoV and now officially named SARS-CoV-2 and COVID-19 has caused major outbreaks of deadly pneumonia in the 21st century has began in Wuhan, China in late 2019 and now become a destructive to global health and therefore the utmost need of the hour is to develop therapeutic candidates or vaccines against it (Zhu et al., 2020). Numerous corona viruses, first discovered in domestic poultry in the 1930s, 2002 and 2012 cause respiratory, gastrointestinal, liver, and neurologic diseases in animals. Only 7 corona viruses are known to cause disease in humans. There is an urgent need to identify specific targets to design promising therapeutic agents against severe acute respiratory syndrome coronavirus aetiological agent of coronavirus disease 2019 (COVID-19) characterised by pulmonary infection in humans. The need exists for additional treatment options addressing antiviral replication, and against SARS-CoV-2. Virus entry and replication strategies are potential targets for antiviral drug treatments. Since NF-κB pathway is often targeted by viral pathogens to enhance viral replication, host cell survival and host immune evasion. Viruses may activate or suppress NF-kB (Marta et al., 2014). There have many studies on SARS-COV since 2002-2003 SARS epidemics. SARS-COV2 (COVID-19) belongs to the same family of corona viruses and shares many similarities (3), including SARS-CoV-1. Here we discuss the possible mechanisms of NFκB inhibitor (SC75741) interference with the SARS-CoV-2 replication cycle.

Key words: NF-kB; SARS-CoV-2; SC75741; COVID-19; ACE-II

Introduction: Nuclear factor kappa B (NF-κB) transcription factors regulate several important physiological processes, including inflammation and immune responses, cell growth, apoptosis, the expression of certain viral genes and Activation of the NF-κB pathway is involved in the pathogenesis of chronic inflammatory diseases, such as asthma, rheumatoid arthritis. NF-κB commonly regarded as a major antiviral factor NF-kB is commonly regarded as a major antiviral factor because it regulates the expression of inflammatory cytokines, chemokines and immunoreceptors. It has been also evidenced that activation of the NF-B signaling pathway represents a major contribution to the inflammation induced after SARS-CoV-1 infection and that NF-B inhibitors are promising antivirals in infections caused by SARS-CoV-1 and potentially other pathogenic human corona viruses. Most important, treatment with drugs that inhibited NF-B activation led to a reduction in inflammation and lung pathology in both SARS-CoV-1 infected cultured cells and mice and significantly increased mouse survival after SARS-CoV-1 infection. Novel NF-kB inhibitor SC75741 significantly protects mice against infection with highly pathogenic avian influenza-A viruses of the H5N1 and H7N7 subtypes. Moreover, Zhao et al. reported that SARS-CoV and MERS-CoV upregulate the expression of ACE-II (Angiotensin converting enzyme-II) in lung tissue, a process that could accelerate their replication and spread. Furthermore, stimulation of the NF-κB activation pathway by phosphorylation of p65 was attenuated by ACE2 inhibitor (Zhao et al., 2020).

COVID 19 activates NF-kB pathway, like MERS and SARS-COV (Marta et al., 2014). SARS-COV virus has been studied in vitro and in mice and was shown to promote inflammatory mediators in vitro and in vivo through actions on NF-kB. Levels of NF-kB were higher in lungs of (recombinant SARS (rSARS)-infected mice. Inhibitors of NF-kB improved survival of BALB/c mice and reduced rSARS-COV-induced inflammation, without influencing viral titers

(Cao et al., 2020). NF-kB is specifically induced by SARS-COV S protein to produce inflammatory mediators that are associated with ARDS in SARS in vitro (Dosch et al., 2009). NF-kB pathway has complex interactions with interferons. Suppression of NF-kB may enhance IFN-mediated antiviral activity (Pfeffer, 2011). In the crosstalk between inflammation and cardiovascular diseases, the transcription factor NFκB seems to be a key player since it is involved in the development and progression of both inflammation and cardiac and vascular damage (Antonella et al., 2019) and Some of deaths due to COVID 19 are due to cardiac involvement (Chen et al., 2020). In addition to many substances that have been described to inhibit NF-kB and hence may be candidates for attentuating inflammation responses in SARS-COV2 infection (Epinat and Gilmore and Herscovitch, 2006), SC75741 may be proposed as an adjunct treatment. SC75741 has been found to have broader anti-inflammatory and anti-tumor mechanisms than what has been described historically as an antiallergy and mast cell stabilizer (Ehrhardt et al., 2013). Most important, treatment with drugs that inhibited NF-B activation led to a reduction in ACE-II experession and consequently downregulation of inflammation and lung pathology in both SARS-CoV-1 infected cultured cells and mice and significantly increased mouse survival after SARS-CoV-1 infection (Ji et al., 2011). On recent study also demonstrated that chloroquine also intersferes with ACE2 receptor glycosylation thus preventing SARS-CoV-2 binding to target cells (Devaux et al., 2020; Gao et al., 2020). SC75741 has been found to be effective in reducing inflammation pathways in several other diseases (Wolf et al., 2002; Haasbach et al., 2013).

In **summary**, NF-kB inhibitor SC75741, may be included as part of the treatment of COVID 19 patient at different stages in their infection, mild, moderate or severe since this molecule was previously described as a potent inhibitor of most viruses, including SARS-CoV-1, and effective in decreasing inflammation, in Acute respiratory distress syndrome (ARDS), and cytokine storm in SARS-CoV-1 patients. It may also reduce viral entry, replication and systemic inflammation, in particular cardiac inflammation.

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