Letter to the Editor

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Can sulfasalazine as an old drug with immunomodulatory and anti-inflammatory effects be effective in COVID-19?

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Coronavirus disease-2019 (COVID-19) is associated with different clinical manifestations; among all, acute respiratory distress syndrome (ARDS) is the most dangerous [1]. It has been reported that this fundamental complication of COVID-19 is related to the multiple pathways like activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway [2], cytokine storm [3], oxidative stress, and increased inflammation [4]. As the COVID-19 pandemic rapidly evolves and expands, international scientific efforts are done in order to find an effective and safe drug for this newly emerged virus. However, this process is a time-consuming and complex challenge. Therefore, it might be logical to investigate the effects of drugs with previously approved anti-inflammatory and anti-oxidative effects in COVID-19 patients [5, 6]. Sulfasalazine is an old and safe disease-modifying anti-rheumatic drug (DMARD) that is applied for the treatment of different types of inflammatory diseases such as rheumatoid arthritis. Furthermore, this agent is also used for the treatment of other auto-immune disease such as ulcerative colitis [7]. The positive point of Sulfasalazine is that this drug has a low immunosuppressive effect. Previous studies have reported that an immune regulatory impact driven by sulfasalazine or its metabolite 5-aminosalicylic acid (5-ASA) against other RNA viruses [8]. Considering the immunomodulatory properties, various *in vitro* studies have indicated that sulfasalazine inhibits the release of cytokines produced by different cell

types [7, 9, 10]. Sulfasalazine exerts strong suppressive effect on polymorphonuclear leukocytes (PMN), moderate inhibitory effect on mononuclear cells (MNC). These suppressive effects include curbing PMN phagocytosis as well as inhibition of their autocrine interleukin (IL)-8 production and functional inhibition of MNC [11]. IL-8 is a powerful pro-inflammatory cytokine with essential role in the activation of neutrophils during inflammation, and, given the frequent neutrophilia reported in patients infected with SARS-CoV-2, it is probable that this cytokine involved in COVID-19 pathophysiology. IL-8 plasma levels were increased in both severe and mild COVID-19 patients and elevated with this viral infection progression [12]. It has been reported that sulfasalazine could reduce the level of IL-8 in the inflammatory condition [13]. In addition T-cell cytokines, such as IL-2 are affected by sulfasalazine [14] and those produced by monocytes or macrophages, including IL-1, IL-6, IL-12 and tumor necrosis factor (TNF)- α [7, 9, 11]. It has been reported that serum TNF- α level is extremely increased in patients with COVID-19 and has direct relation with the severity of this disease [15]. Furthermore, sulfasalazine is a potent and specific inhibitor of the transcription factor NF-kappaB [16]. This drug has been reported to inhibit random migration and chemotaxis of neutrophils, and to decrease proteolytic enzyme and superoxide over-production in several studies [17]. Other potential anti-inflammatory effects include an inhibitory effect on prostaglandin E2 synthetase activity, inhibition of release of lysosomal enzyme from macrophages, inhibition of the extracellular release of proinflammatory phospholipase A2 and rapid apoptosis of neutrophils [18]. Various studies have indicated its activities including neuroprotective, antioxidant, anti-inflammatory and anticancer properties [16, 19–21]. Sulfasalazine's considerable immunomodulatory, anti-inflammatory and anti-oxidative effects could be beneficial in the management of COVID-19 patients, especially in reducing its respiratory symptoms – multiorgan damage and ARDS (Figure 1). As mentioned previously, COVID-19 induced ARDS arises as a result of cytokine storm with IL-6 and other cytokines which have

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Figure 1: The potential beneficial effects of sulfasalazine in patients with COVID-19. SARS-CoV-2 infection leads to cytokine storm, activation of NF-κB and induction of oxidative stress. Immunomodulatory, anti-inflammatory and anti-oxidative effects of sulfasalazine could ameliorate the severity of SARS-CoV-2 infection.

an essential role in effecting tissue damage and subsequent mortality [22]. I have observed that sulfasalazine considerably decrease the secretion of cytokines such as TNF- α , IL-2 and IL-6; hence, could offer a potential role in ameliorating COVID-19 associated cytokine release syndrome [7]. The other beneficial effect of sulfasalazine in COVID-19 could be attributed to its anti-oxidative effects which have been reported in various studies. Common adverse effects, including gastrointestinal effects, rash, dizziness and headache which are subside following discontinuation [23]. Since the most COVID-19 patients that are not hospitalized will be requiring therapy for a few days only, the potential use of sulfasalazine in these patients is unlikely to be fraught with considerable issues. In conclusion, based on the available information on anti-inflammatory and immunomodulatory effects of sulfasalazine, considering the fact that sulfasalazine is a safe drug, we suggest randomized placebo controlled-trials on the effects of this drug on SARS-CoV-2 infection in order to respond to this question that is sulfasalazine beneficial for patients with COVID-19 or not?

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