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## Etoricoxib may inhibit cytokine storm to treat COVID-19

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### ABSTRACT

The worldwide spread of COVID-19 has caused an unprecedented disaster. The emergence of COVID-19-mediated cytokine storm is one of the most important contributors to the development of acute and severe illness in patients. At present, there is an urgent need for drugs that can inhibit cytokine storm to treat COVID-19. In the absence of specific drugs and vaccines, it is important to screen existing drugs as potential treatments. This article introduces a potential repositioning of the existing drug etoricoxib, which may inhibit cytokine storm to treat COVID-19 through reducing the activity of Cyclooxygenase-2 in the conversion of arachidonic acid to prostaglandin.

### Hypothesis background

Since the outbreak of COVID-19 in 2019, a worldwide pandemic has caused tens of millions of infections and more than one million deaths. Most patients experience only mild symptoms, such as fever, cough or muscle aches [1]. Although the prognosis of most patients is good, there are still a large number of patients who develop sudden deterioration in the later stage of the disease, acute respiratory distress syndrome or multiple organ failure, which is an important cause of death from COVID-19 [1]. Studies have shown that abnormal secretion of a large number of proinflammatory mediators in the human body leads to abnormal immune responses caused by cytokine storm, which is one of the important reasons for this sudden deterioration [2].

### Statement of hypothesis

Existing data indicate that COVID-19 causes the secretion of a large number of proinflammatory factors, such as interleukins (IL-6, IL-1 $\beta$ , IL-12, IL-18, and IL-33), tumor necrosis factors, (TNF- $\alpha$ ), and chemokines, which are considered important factors leading to death in COVID-19 patients [2]. Among them, IL-6, IL-1 $\beta$ , and TNF- $\alpha$  are critical factors. IL-6 is considered to be the most important factor associated with cytokine storm, and the level of IL-6 in patients can be increased up to 1000 times that of normal individuals, while IL-1 $\beta$  and TNF- $\alpha$  can be increased up to 100 times that of normal individuals. Related research also supports that the level of IL-6 has a high correlation with death due to COVID-19 [3]. This evidence shows that suppressing cytokine storm may be an important way to improve the survival rate of COVID-19

patients.

Cyclooxygenase (COX) inhibitors decrease the conversion of arachidonic acid to prostaglandin by reducing COX activity, thereby blocking the inflammatory cascade caused by prostaglandins, and can potentially inhibit cytokine storm [4]. COX has two isoenzymes, of which COX-1 is widely expressed, while COX-2 is only expressed in pathological conditions. Etoricoxib is a selective COX-2 inhibitor. The selective effect of etoricoxib can be better than that of traditional nonselective COX inhibitors [5]. Based on the above conditions, etoricoxib can be considered for repositioning as a potential drug to suppress cytokine storm to treat COVID-19.

### Support for the hypothesis

Despite the fact that etoricoxib is still not approved by FDA (which may prevent the use of etoricoxib in the United States), etoricoxib has been approved for marketing in more than 80 countries, most of which suffering from COVID-19 pandemic. Although no serious drug safety issues have been reported, etoricoxib has some side effects, including: nausea, indigestion, diarrhoea, high blood pressure, dizziness, and headache. These side effects are usually mild [6]. So, etoricoxib is considered to have very good drug safety. Additionally, since etoricoxib does not act on COX-1, compared with that of nonselective COX inhibitors, the risk of damage to the lining of the gastric mucosa is greatly reduced, and the potential risk of damage to the regulation of platelet functions, renal hemodynamics and electrolyte balance is also reduced [7]. This finding also indicates that compared with nonselective COX inhibitors, etoricoxib is beneficial to the potential intestinal and renal

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symptoms of COVID-19 patients [3]. Etoricoxib has been used for the treatment of rheumatoid arthritis, psoriatic arthritis, osteoarthritis, ankylosing spondylitis, chronic low back pain, acute pain and gout. Based on above situations, etoricoxib has excellent potential of drug repositioning. Related studies have shown that etoricoxib has the potential to inhibit IL-6, IL-1 $\beta$ , TNF- $\alpha$  and other proinflammatory factors. A study of 11 patients undergoing hip replacement surgery showed that in the etoricoxib treatment group, the serum IL-6 concentration significantly decreased ( $p \leq 0.05$ ) [8]. A study of 51 patients with arthritis showed that in the etoricoxib treatment group, the serum IL-1 $\beta$  concentration and synovial fluid IL-6 concentration were significantly reduced after treatment ( $p = 0.045$  and  $p = 0.019$ , respectively) [9]. It is worth noting that in addition to inhibiting the function of inflammatory factors, there may also have anti-tumor effects. A study on lung tumors in rats showed that after treatment with etoricoxib, the levels of inflammatory factors such as IL-1 $\beta$  and TNF- $\alpha$  were significantly reduced ( $p \leq 0.05$ ), and the tumor was compared with that of the control group. In diseased tissues, etoricoxib is considered to have anti-tumor effects [4]. A study also reported the etoricoxib attenuates high-sugar/fat diet-induced mammary carcinogenesis and decreases mammary tissue levels of IL-6 in mice fed high-sugar/fat diet ( $p \leq 0.05$ ) [10].

### Test for the hypothesis

To test this hypothesis, we suggest to first a systematically study where a small group of patients at high risk for COVID-19 is given etoricoxib treatment at dose similar to that used in previous study [11]. During this study, Lung lesions monitoring (by CT scan) would be regularly executed and cytokine level (especially the level of IL-6) would be serially and systematically monitored. Through data analysis, should preliminary results be ameliorated with this treatment plan, then a randomized and prospective double blinded study should be conducted prior to large scale adaptation of this treatment plan [12]. Recently, we noticed that a study of COVID-19 patients who received clinical benefit after treatment with etoricoxib has been reported. This is an exciting study that indicated the reduction of IL-6 level after etoricoxib treatment. However, the number of patients in this group who receiving the IL-6 level monitoring in this study is small, while samples collection for IL-6 levels was not done systematically before and after intervention, which indicate the necessary of more studies [11].

It must be mentioned that the combined use of drugs is a common treatment option [13]. So the combined use of etoricoxib and other anti-cytokine storm drugs is a potential treatment option to inhibit cytokine storm to treat COVID-19. At present, some drugs have been chosen, like IL-6 inhibitors (like Tocilizumab) [14], steroids [15], etc. IL-6 inhibitors may be a safe and effective drug, which mainly decreases IL-6 levels through antigen-antibody effects, but the high price may limit the application [16,17]. Steroids could eliminate a wide range of cytokines, but such elimination will also decline some kinds of cytokines which need to be maintained at normal or positive levels [18]. Etoricoxib may be used in combination with IL-6 inhibitors to decrease IL-6 level through different targets to inhibit cytokine storm to treat COVID-19 and reduce the amount and cost of IL-6 inhibitors. Also, etoricoxib may be combined with steroids to decrease IL-6 level while ensuring reasonable levels of some kinds of cytokines. Recently, Janus kinase inhibitor (like Ruxolitinib) is also a candidate that can inhibit the cytokine storm to treat COVID-19 [19]. The mechanism of action is to block the signal transduction of IL-6 [20]. The combination of Janus kinase inhibitor and etoricoxib may achieve good results by blocking different targets of IL-6.

### Conclusion

Various properties indicate etoricoxib may have the potential to inhibit the cytokine storm to treat COVID-19. Therefore, it is reasonable

to consider conducting a comprehensive evaluation of etoricoxib to establish the repositioning of this drug as a treatment for COVID-19.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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