

Raloxifene and Bazedoxifene Could Be Promising Candidates for Preventing the COVID-19 Related Cytokine Storm, ARDS and Mortality

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Abstract. *The FDA-approved drugs raloxifene and bazedoxifene could be among the best candidates to prevent mortality in severe COVID-19 patients. Raloxifene and bazedoxifene inhibit IL-6 signaling at therapeutic doses, suggesting they have the potential to prevent the cytokine storm, ARDS and mortality in severe COVID-19 patients, as is being shown with humanized antibodies blocking IL-6 signaling. In addition, raloxifene and bazedoxifene are selective estrogen receptor modulators with strong antiviral activity.*

In April 2020, we were the first to propose bazedoxifene as one of the most promising candidates to inhibit the IL6/cytokine storm, ARDS and mortality axis in COVID-19 patients with pneumonia (1, 2). Bazedoxifene and raloxifene, which belongs to the same class, were developed as estrogen analogs for the treatment of postmenopausal osteoporosis. However, these drugs also interact with GP130, a part of the IL6 receptor (3, 4), and prevent the binding of IL6 to its receptor.

Bazedoxifene and raloxifene exhibit anti-inflammatory activity in arthritis (5) and due to their anti-IL6 signaling activity were also found to have anticancer effects, directly associated to their verified potential to inhibit IL6 signaling in animals, at doses similar to therapeutic doses in humans

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(6). Bazedoxifene and raloxifene may therefore represent cheaper and easier alternatives for large scale production, compared to humanized IL6 signaling antibodies for the treatment of severe COVID-19-related lung complications. Moreover, the selective estrogen receptor modulator function of bazedoxifene and raloxifene could be effective against SARS-CoV-2 entry and replication. Consistently, the *in vitro* preliminary results indicate that bazedoxifene and raloxifene have strong direct antiviral activity against COVID-19 (7, 8).

In addition, raloxifene was identified as a molecule of interest by the Exscalate4CoV consortium, using a unique combination of high-performance computing and AI with biological processing. The consortium virtually tested 400 000 molecules using its supercomputers. 7 000 molecules were preselected and further tested *in vitro*. Raloxifene emerged as a promising molecule; according to the project, it could be effective in blocking the replication of the virus in cells, and could thus hold up the progression of the disease (9), further confirming our proposal.

To conclude, raloxifene and bazedoxifene are among the best candidates to prevent the cytokine storm, ARDS and mortality in severe COVID-19 patients, with the further benefit of a strong antiviral activity.

Conflicts of Interest

The Authors declare no competing interests.

Authors' Contributions

K.S., D.R. and J.B. collected data and prepared the article.

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