COVID-19: combining antiviral and anti-inflammatory treatments

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Both coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) are characterised by an overexuberant inflammatory response and, for SARS, viral load is not correlated with the worsening of symptoms.[1,2] In our previous Correspondence to *The Lancet*,[3] we described how BenevolentAI's proprietary artificial intelligence (AI)-derived knowledge graph,[4] queried by a suite of algorithms, enabled identification of a target and a potential therapeutic against SARS coronavirus 2 (SARS-CoV-2; the causative organism in COVID-19). We identified a group of approved drugs that could inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells (appendix). The drug targets are members of the numb-associated kinase (NAK) family—including AAK1 and GAK—the inhibition of which has been shown to reduce viral infection in vitro.[5,6] Baricitinib was identified as a NAK inhibitor, with a particularly high affinity for AAK1, a pivotal regulator of clathrin-mediated endocytosis. We suggested that this drug could be of use in countering SARS-CoV-2 infections, subject to appropriate clinical testing.

To take this work further in a short timescale, a necessity when dealing with a new human pathogen, we re-examined the affinity and selectivity of all the approved drugs in our knowledge graph to identify those with both antiviral and anti-inflammatory properties. Such drugs are predicted to be of particular importance in the treatment of severe cases of COVID-19, when the host inflammatory response becomes a major cause of lung damage and subsequent mortality. Comparison of the properties of the three best candidates are shown in the table. Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. All three are powerful anti-inflammatories that, as JAK–STAT signalling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines (including interferon-γ) typically observed in people with COVID-19.[2] Although the three candidates have similar JAK inhibitor potencies, a high affinity for AAK1 suggests baricitinib is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile.[7] The most significant side-effect seen over 4214 patient-years in the clinical trial programmes used for European Medicines Agency registration was a small increase in upper respiratory tract infections (similar to that observed with methotrexate), but the incidence of serious infections (eg, herpes zoster) over

See Online for appendix

	Baricitinib	Ruxolitinib	Fedratinib
Daily dose, mg	2–10	25	400
Affinity and efficacy: K_d or IC_{50}, nM*			
AAK1†			
Cell free	17	100	32
Cell	34	700	960
GAK†			
Cell free	136	120	1
Cell	272	840	30
BIKE†			
Cell free	40	210	32
Cell	80	1470	960
JAK1			
Cell free	6	3	20
Cell	12	20	600
JAK2			
Cell free	6	3	3
Cell	11	21	100
JAK3			
Cell free	>400	2	79
Cell	>800	14	2370
TYK2			
Cell free	53	1	20
Cell	106	7	600
Pharmacokinetics			
Plasma protein binding	50%	97%	95%
C_{max} (unbound), nM	103‡	117	170
Safety: tolerated dose	≤10 mg/day	≤20 mg twice daily	≤400 mg/day

See regulatory approval documents for further information on these drugs. K_d=dissociation constant. IC_{50}=half-maximal inhibitory concentration. C_{max}=maximum serum concentration. *All values are IC_{50} except the cell free values for AAK1, GAK, and BIKE; "cell free" values indicate inhibitory activity against purified protein in biochemical assay; "cell" values indicate enzyme-inhibitory activity inside a cell. †In the absence of direct measurements of drug inhibition in cells, the predicted cell affinity and efficacy values are derived from the ratio of each compound for their primary target; for example, for baricitinib, IC_{50} AAK1[cell] = (IC_{50}AK1[cell] / IC_{50}AK1[cell free]) × IC_{50}AAK1[cell free]. ‡At a 10 mg dose.

Table: **Properties of three antiviral and anti-inflammatory candidate drugs**

52 weeks' dosing was small (3·2 per 100 patient-years), and similar to placebo.[7] Use of this agent in patients with COVID-19 over 7–14 days, for example, suggests side-effects would be trivial.

Other AI-algorithm-predicted NAK inhibitors include a combination of the oncology drugs sunitinib and erlotinib, shown to reduce the infectivity of a wide range of viruses, including hepatitis C virus, dengue virus, Ebola virus, and respiratory syncytial virus.[5,6] However, sunitinib and erlotinib would be difficult for patients to tolerate at the doses required to inhibit AAK1 and GAK. By contrast, at therapeutic doses used for the treatment of patients with rheumatoid arthritis, the free plasma concentrations of baricitinib are predicted to be sufficient to inhibit AAK1, and potentially GAK, in cell-based assays.

The predicted inhibition of clathrin-mediated endocytosis by baricitinib is unlikely to be observed with other anti-arthritic drugs or JAK inhibitors. Our analysis of the closely related JAK inhibitors ruxolitinib and fedratinib (table) illustrates that the predicted unbound plasma exposure required to inhibit the enzymes needed for clathrin-mediated endocytosis greatly exceeds the currently tolerated exposures used therapeutically. These drugs are, therefore, unlikely to reduce viral infectivity at tolerated doses, although they might reduce the host inflammatory response through JAK inhibition. Intriguingly, another JAK inhibitor, tofacitinib, shows no detectable inhibition of AAK1. The high affinity of baricitinib for NAKs, its anti-inflammatory properties, and its ability to ameliorate associated chronic inflammation in interferonopathies,[8] together with its advantageous pharmacokinetic properties, appear to make it a special case among the approved drugs.

In addition, the potential for combination therapy with baracitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters. Furthermore, there is the potential for combining baricitinib with the direct-acting antivirals (lopinavir or ritonavir and remdesivir) currently being used in the COVID-19 outbreak, since it has a minimal interaction with the relevant CYP drug-metabolising enzymes. Combinations of baricitinib with these direct-acting antivirals could reduce viral infectivity, viral replication, and the aberrant host inflammatory response. This work demonstrates that the use of an AI-driven knowledge graph can facilitate rapid drug development.

JS is editor-in-chief of *Oncogene*. JS has previously sat on a number of scientific advisory boards, including BenevolentAI, and consults with Lansdowne partners and Vitruvian; he now sits on the Board of Directors for BB Biotech Healthcare Trust and chairs Xerion Healthcare. All other authors are employees of BenevolentAI. Events in relation to the COVID-19 outbreak are evolving rapidly, and we make our initial thoughts available in this Comment in good faith and to assist in the global response. Our early investigations and suggestions require further detailed work and analysis and should not be relied on as constituting any kind of medical or other advice or recommendation.

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