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Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

UNIVERSITÀ DEGLI STUDI DI MILANO

Mechanism of Baricitinib supports artificial intelligence-testing in COVID-19 patients

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2 Eli Lilly and Company, Indianapolis, IN, USA
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EMBO Molecular Medicine

- Baricitinib is an oral Janus kinase (JAK) inhibitor that reversibly binds to JAK1 and JAK2. Via a signal transduction pathway involving STAT proteins, baricitinib modulates gene expression in immunological cells.
- Approved by EMA and AIFA for the treatment of moderate to severe active **rheumatoid arthritis RA** in patients with inadequate response or intolerance to DMARDs (monotherapy or in association with MTX) and **atopic dermatitis AD** in patient who are candidates for systemic therapy.
- Dosage: 4 mg q24h (2 mg if ≥ 75 years mg or CrCl 30-60 mL/min).
- Baricitinib reduces IL-6 and CRP levels in patients with RA or AD.

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Correspondence

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Baricitinib as potential treatment for 2019-nCoV acute respiratory disease

Given the scale and rapid spread of the 2019 novel coronavirus (2019-nCoV) acute respiratory disease, there is an immediate need for medicines that can help before a vaccine can be

might block the viral infection process. We identified baricitinib, which is predicted to reduce the ability of the virus to infect lung cells.

Most viruses enter cells through receptor-mediated endocytosis. The receptor that 2019-nCoV uses to infect lung cells might be ACE2, a cell-surface protein on cells in the kidney, blood vessels, heart, and, importantly, lung AT2 alveolar epithelial cells

the inhibition of AAK1.[5] However, these compounds bring serious side-effects, and our data infer high doses to inhibit AAK1 effectively. We do not consider these drugs would be a safe therapy for a population of sick and infected people.

By contrast, one of the six high-affinity AAK1-binding drugs was the janus kinase inhibitor baricitinib, which also binds the cyclin G-associated

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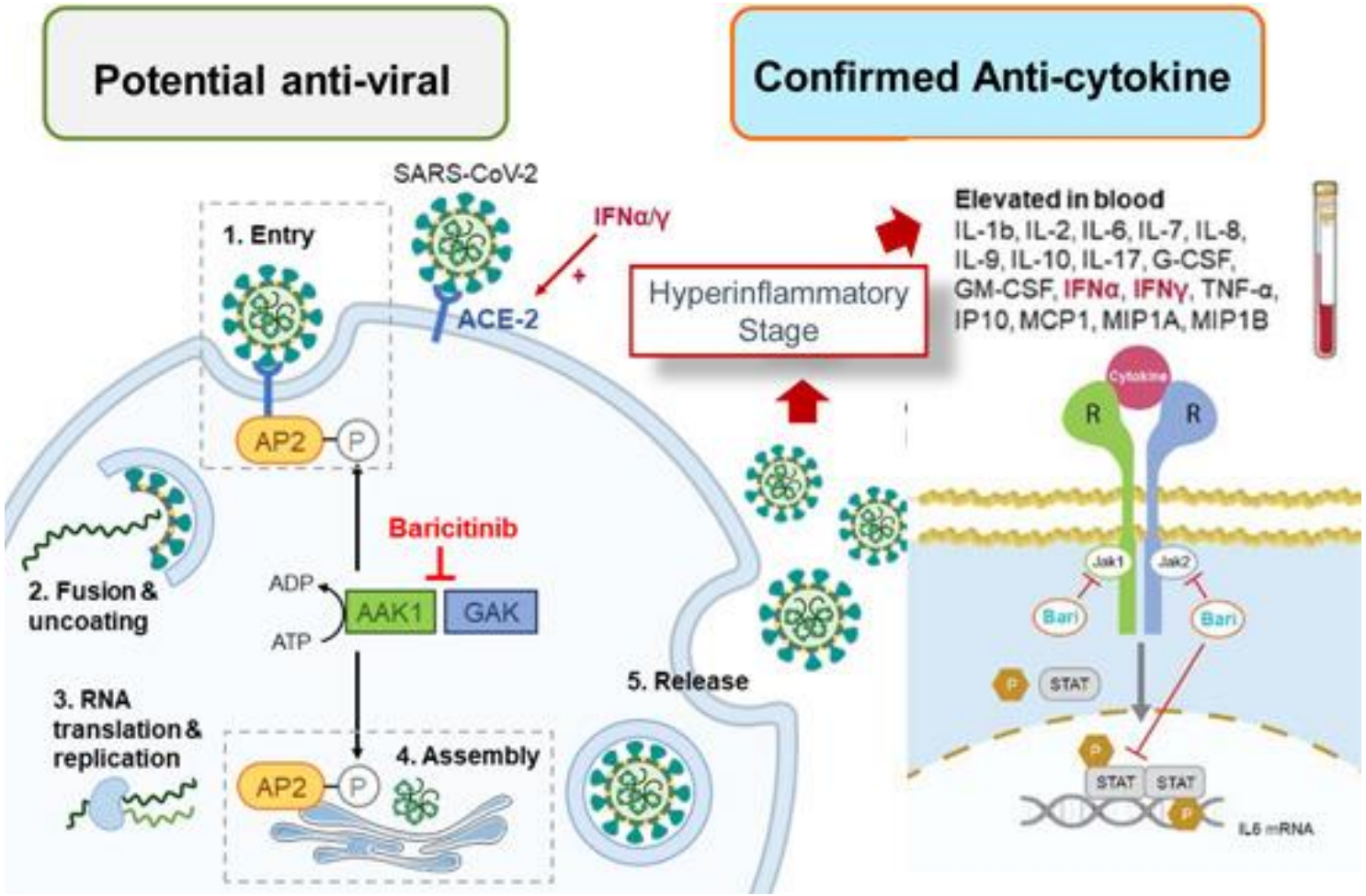
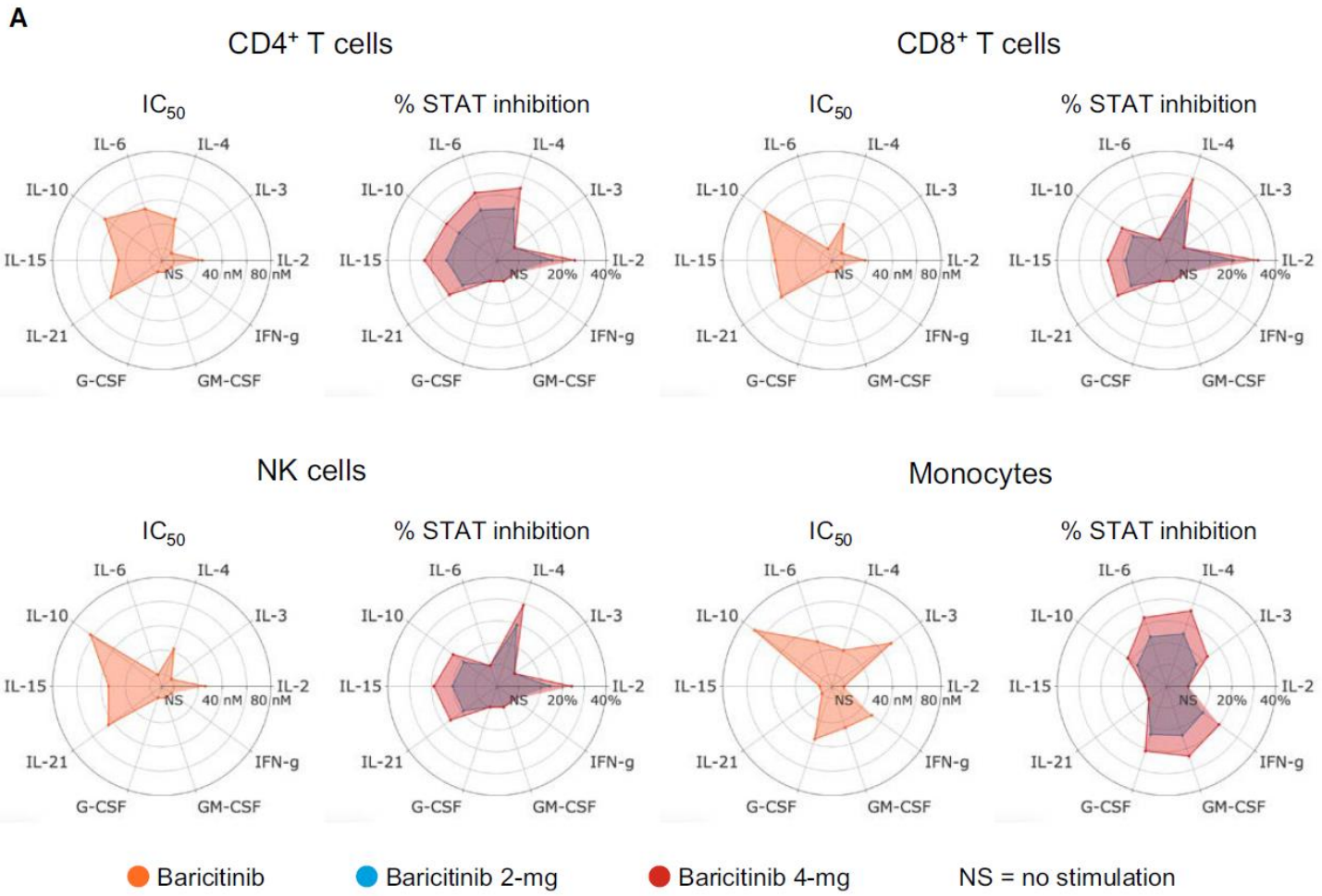
This online publication has been corrected. The corrected version first appeared at thelancet.com on June 18, 2020

THE LANCET

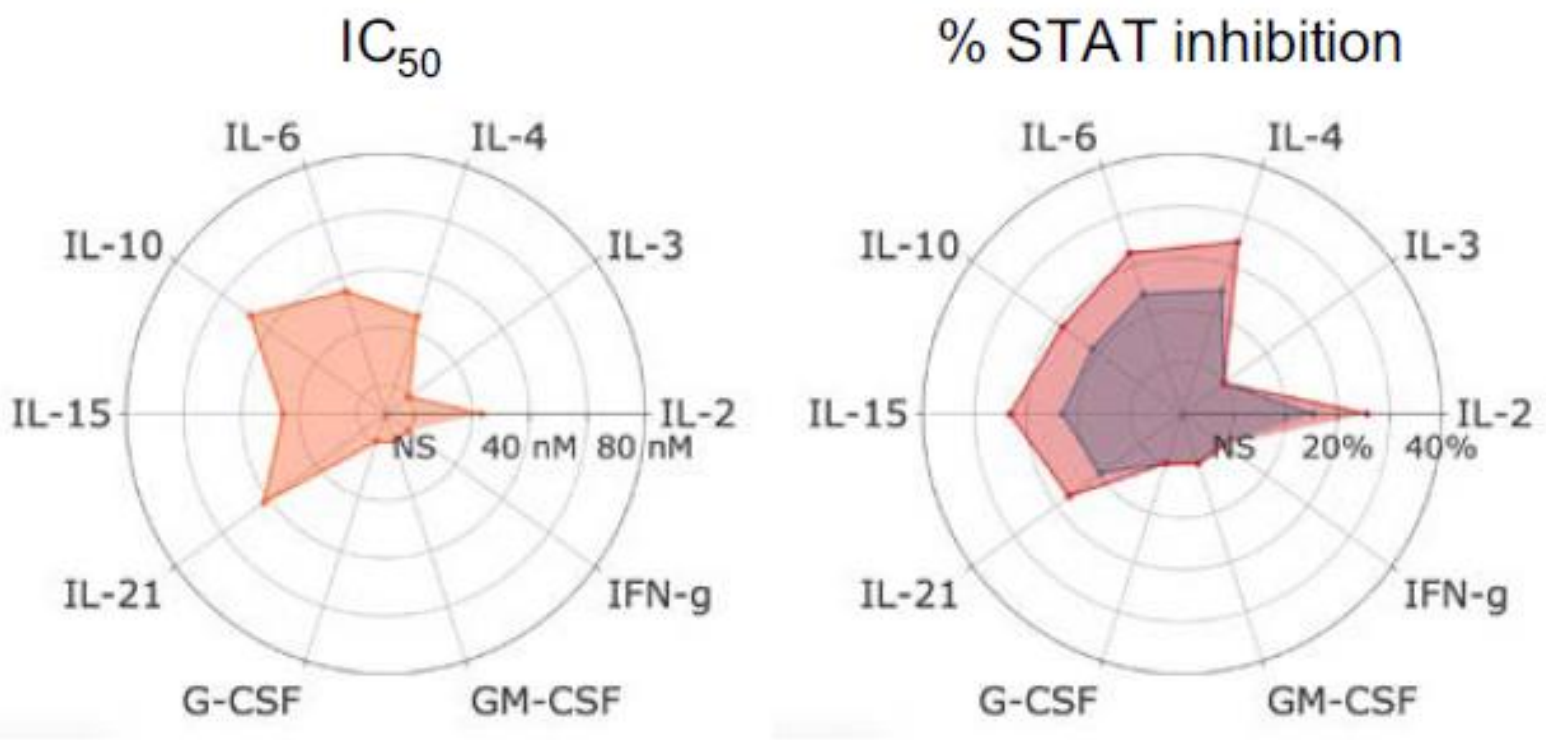

Potential anti-viral
Confirmed Anti-cytokine
SARS-CoV-2
1. Entry
IFNα/γ
ACE-2
AP2
P
Baricitinib
ADP
ATP
AAK1
GAK
2. Fusion & uncoating
3. RNA translation & replication
4. Assembly
5. Release
Hyperinflammatory Stage
Elevated in blood
IL-1b, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM-CSF, IFNα, IFNγ, TNF-α, IP10, MCP1, MIP1A, MIP1B
Cytokine
R
R
Jak1
Jak2
Bari
Bari
STAT
STAT
STAT
IL6 mRNA

Anti-cytokine effect

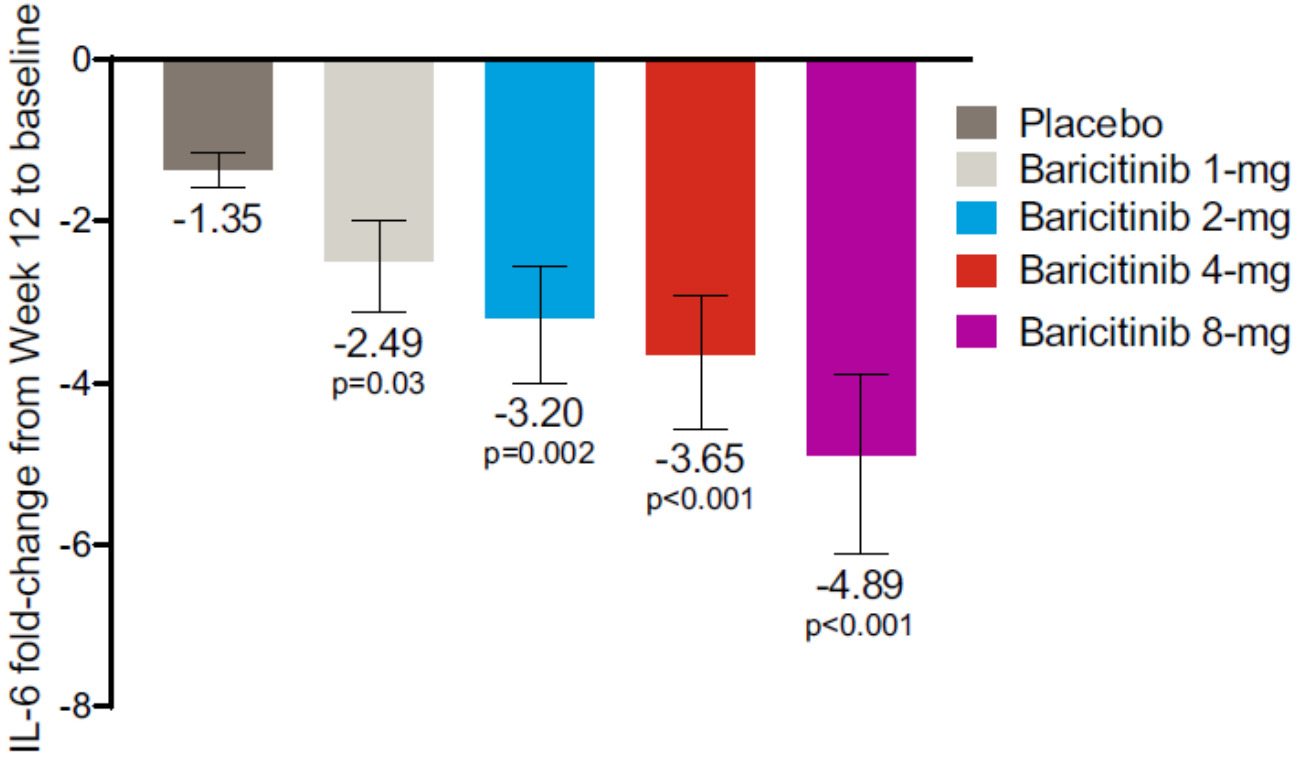


A

CD4⁺ T cells


IC50
IL-6
IL-4
IL-3
IL-2
IFN-g
GM-CSF
G-CSF
IL-21
IL-15
IL-10
NS
40 nM
80 nM
% STAT inhibition
IL-6
IL-4
IL-3
IL-2
IFN-g
GM-CSF
G-CSF
IL-21
IL-15
IL-10
NS
20%
40%

Anti-cytokine effect



- Blood samples from the double-blind, randomized, placebo-controlled, phase 2b study on moderate-to-severe active adult-onset RA, despite stable MTX treatment.
- 12 weeks of treatment.

Tanaka et al. 2016. NCT01469013.

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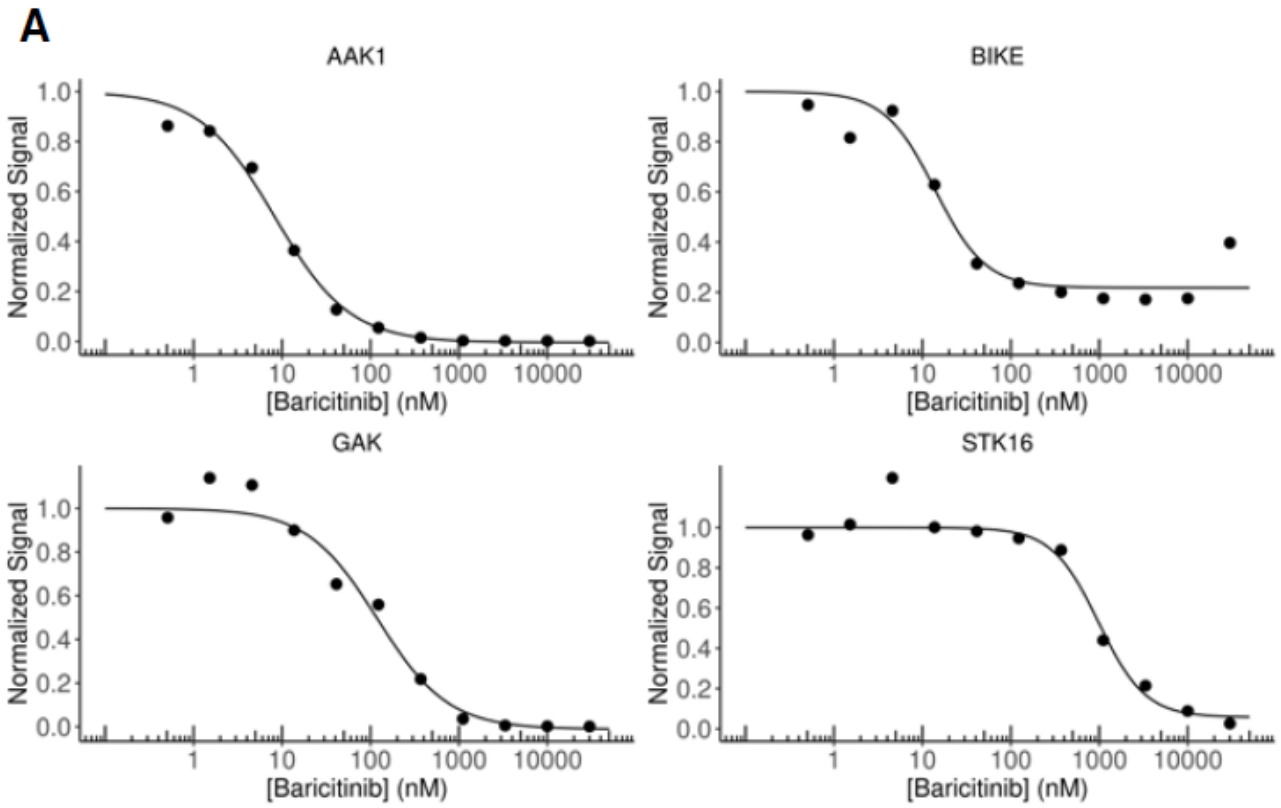
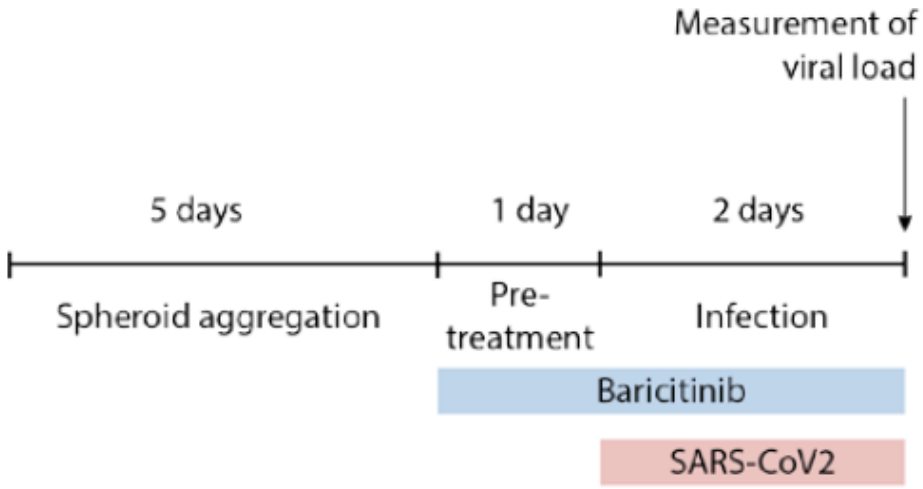
Anti-viral effect



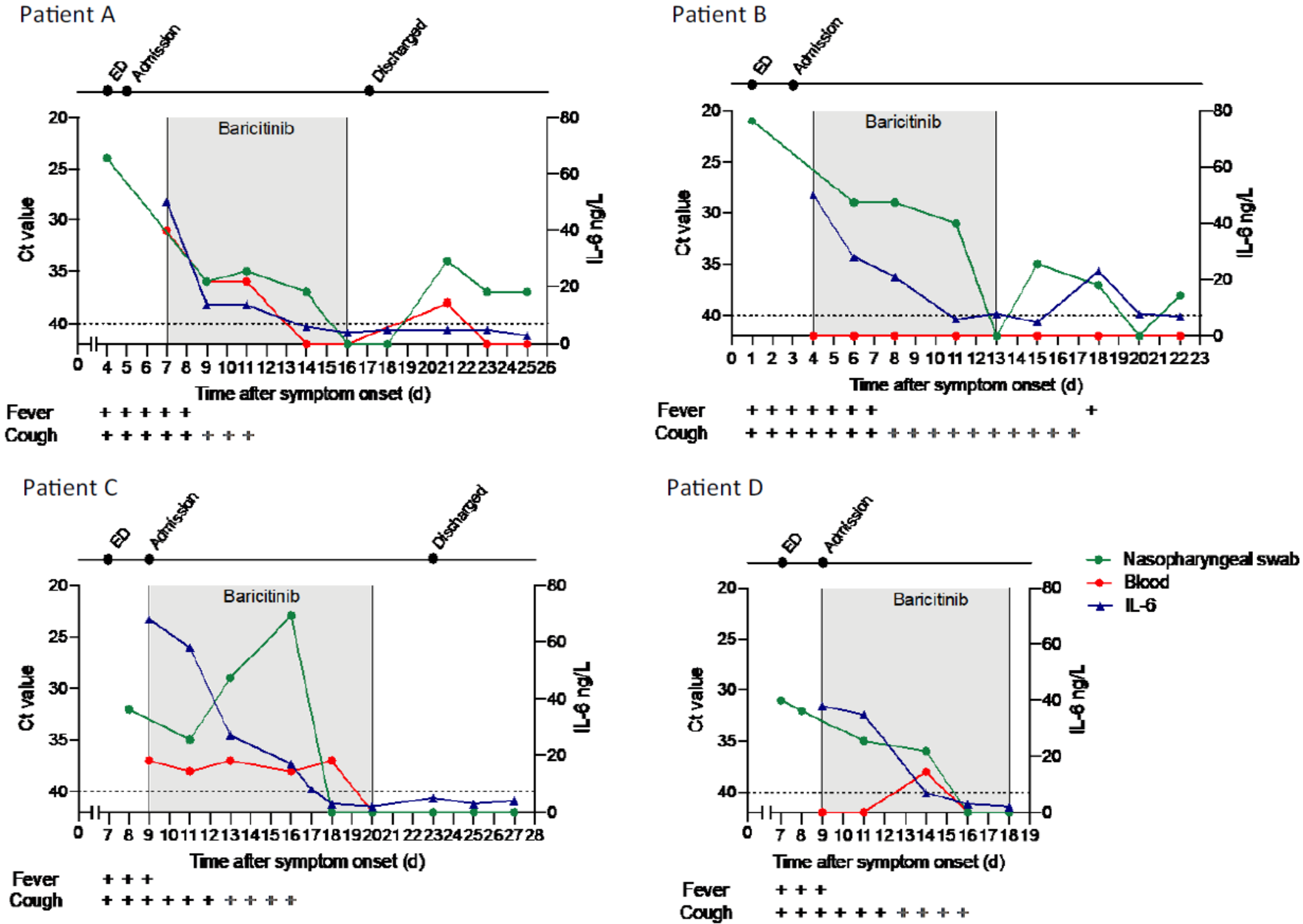
Baricitinib activity demonstrated affinity against NAKs within a [C] range of the approved doses of baricitinib for the treatment of RA.



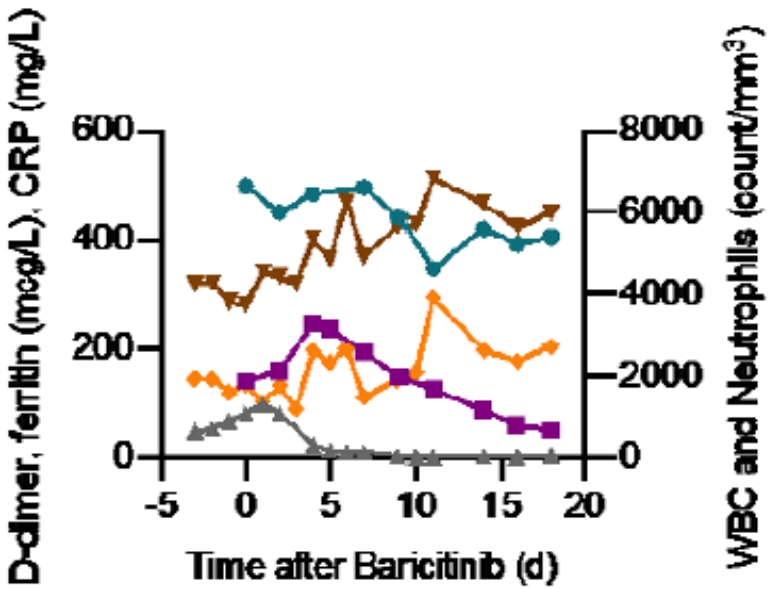
Pretreatment of spheroids with physiologically relevant concentrations of baricitinib significantly reduced viral load by 30–40%.

Our "Fab Four"

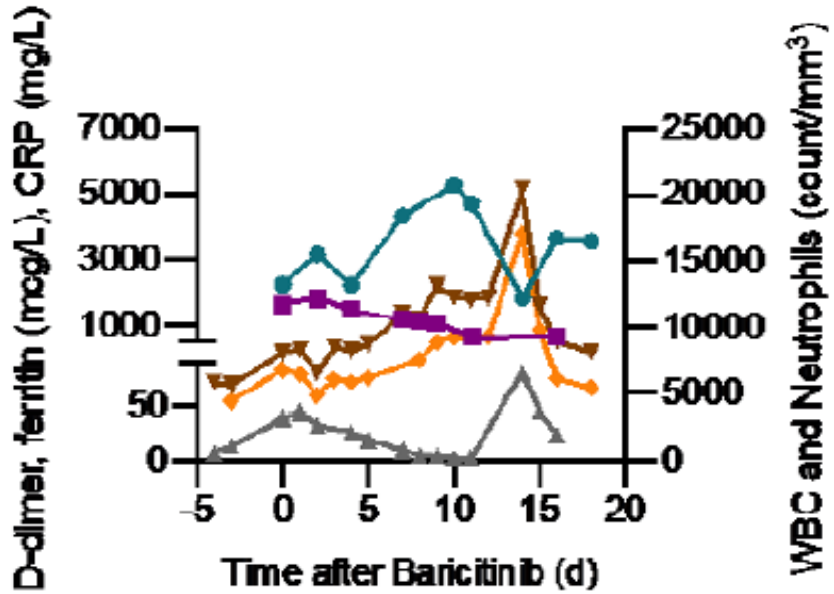
	Patient A	Patient B	Patient C	Patient D
Age (years)	29	76	57	51
Gender	Female	Male	Male	Male
Coexisting conditions	None	AH, COPD, CAD	AH, COPD	Obesity
BMI	22	28	29	35
Medications	Combined oral contraception	Losartan, propranolol, omeprazole, aspirin, LMW heparin	Losartan, hydrochlorothiazide, inhaled beclomethasone	None
Smoking	No	Former	No	No
Data at presentation				
Symptoms	Fever, dry cough, and myalgias	Fever, dry cough	Fever, dry cough, dyspnea	Fever, dry cough, headache
Blood oxygen levels PaO2 (mmHg)	111	81	62	80
Alveolar oxygen gradient (KPa)	0	4.7	12.9	4.9
SpO2 (%)	98	97	94	91
RR/min	26	32	28	28
Baricitinib dose/days on treatment	4 mg for 10 days	2 mg for 10 days	4 mg for 12 days	4 mg for 10 days


Patient A
ED
Admission
Discharged
Baricitinib
Ct value
IL-6 ng/L
Time after symptom onset (d)
Fever
Cough
Patient B
ED
Admission
Baricitinib
Ct value
IL-6 ng/L
Time after symptom onset (d)
Fever
Cough
Patient C
ED
Admission
Discharged
Baricitinib
Ct value
IL-6 ng/L
Time after symptom onset (d)
Fever
Cough
Patient D
ED
Admission
Baricitinib
Ct value
IL-6 ng/L
Time after symptom onset (d)
Fever
Cough
Nasopharyngeal swab
Blood
IL-6

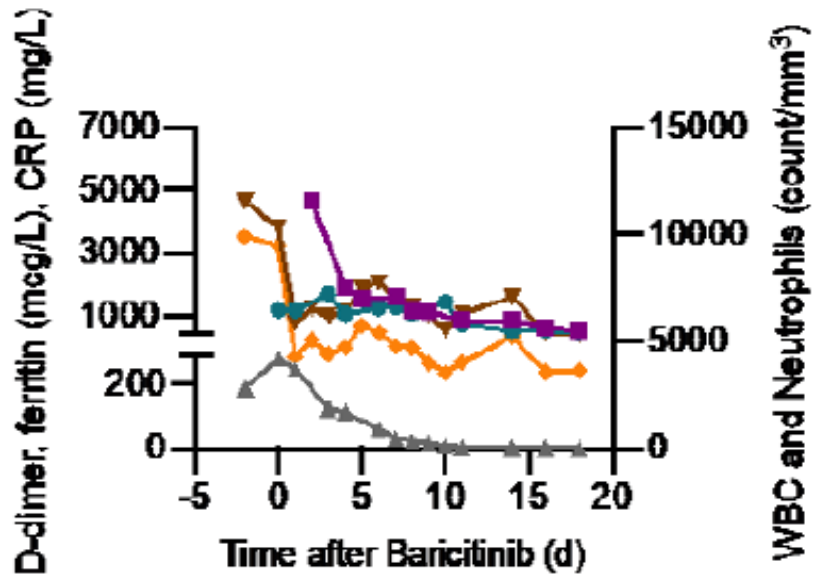
Patient A



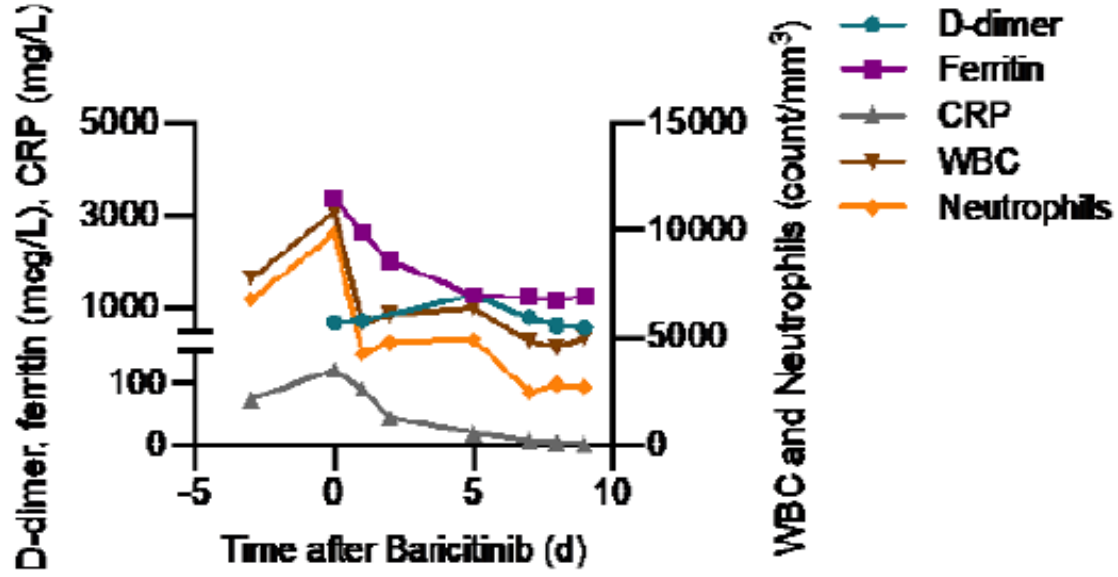
Patient B



Patient C



Patient D

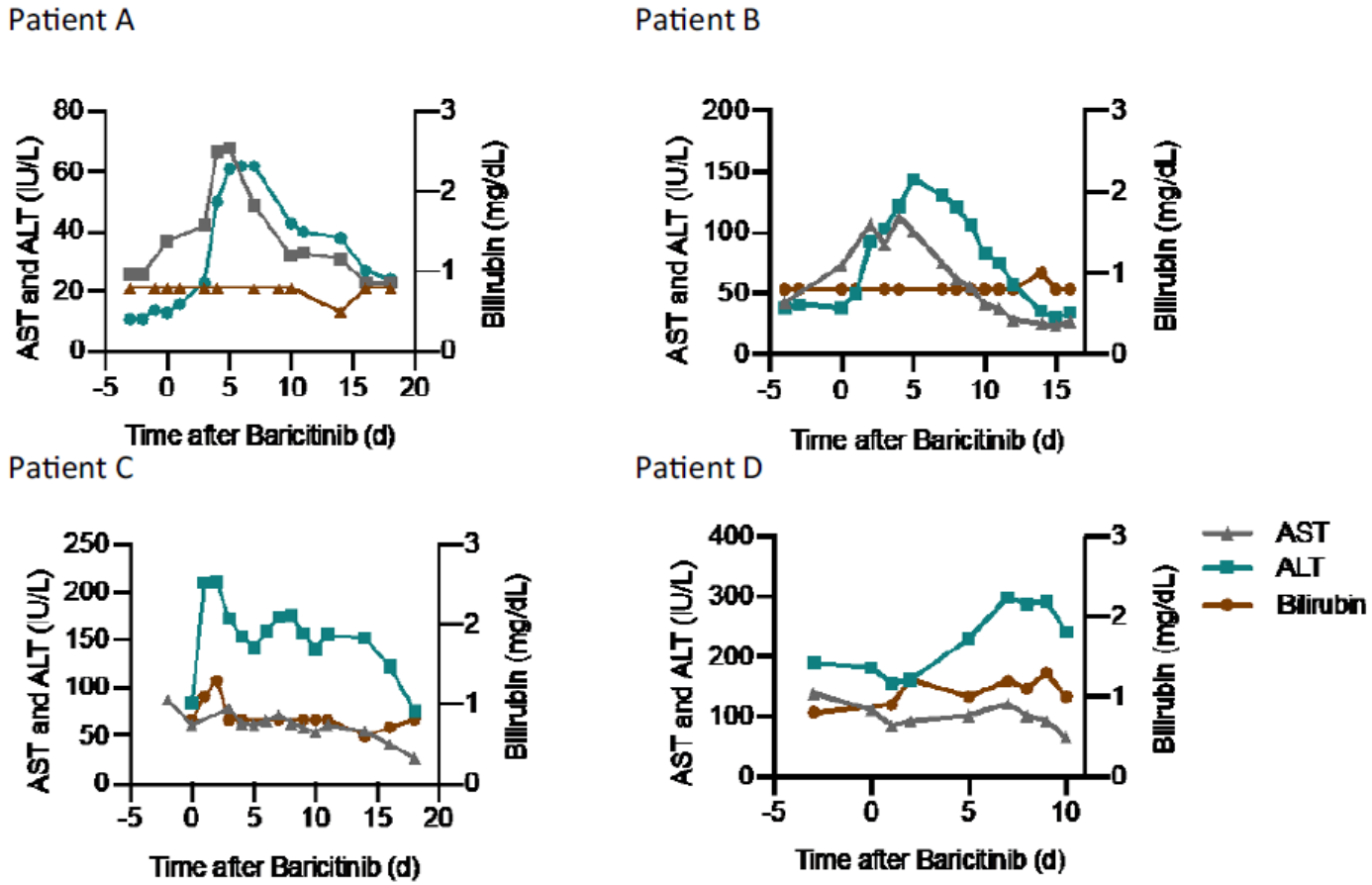


Safety

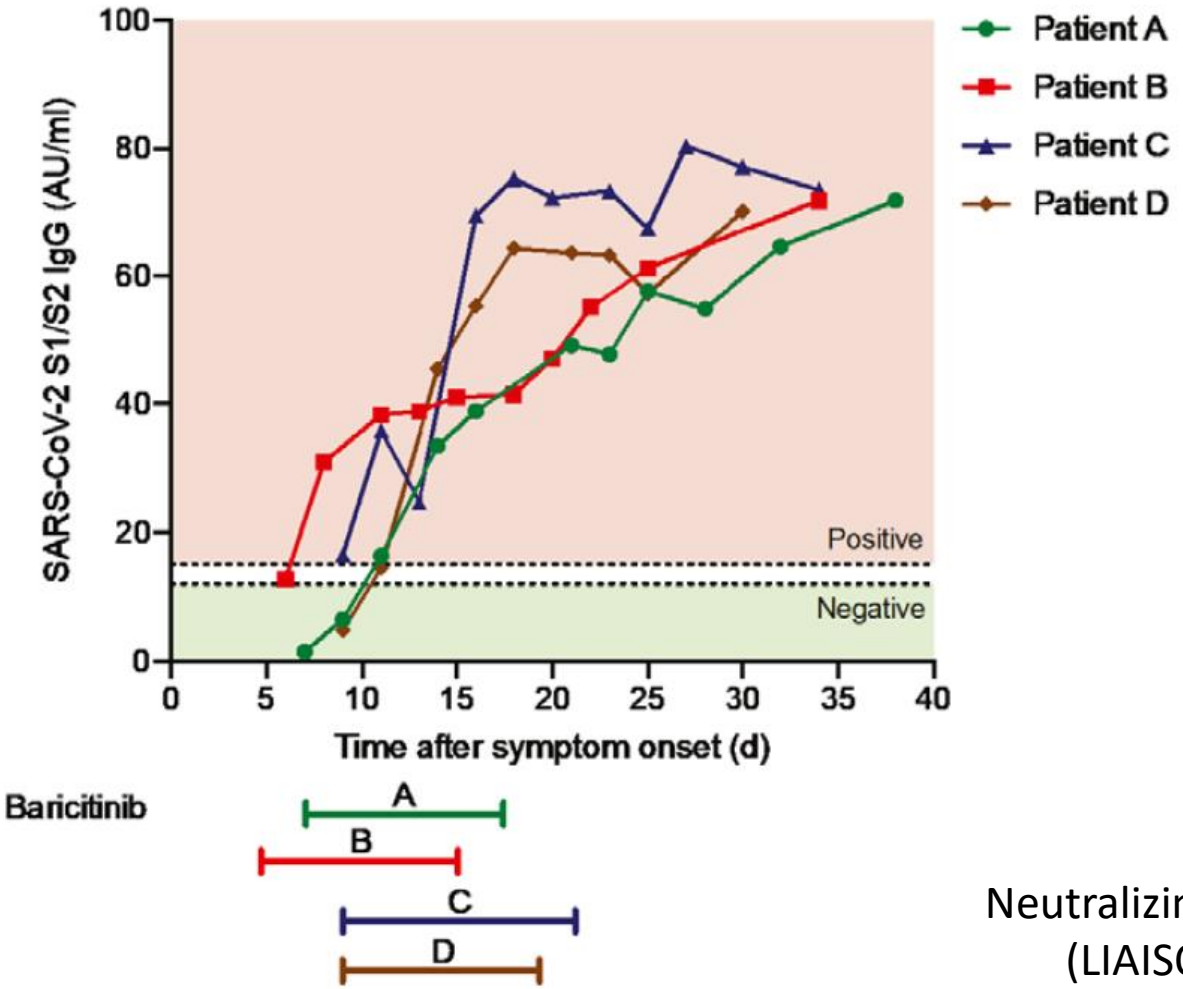
No DVT/PE detected.

Mild and reversable elevation in AST/ALT.

No other adverse reaction detected.



Immune response



All four patients achieved sero-conversion during baricitinib treatment.

Neutralizing antibodies against the S1 and S2 spike proteins of SARS-CoV-2 (LIAISON SARS-CoV-2 S1/S2 IgG Kit, DiaSorin S.p.A., Saluggia, Italy)

Conclusions

- Baricitinib **inhibits cytokines** implicated in COVID-19 cytokine storm.
- Baricitinib **may have an anti-viral effect**, blocking viral entry and propagation.
- In a pilot study, treatment with baricitinib was associated with improvement in clinical, radiological, and immunovirological parameters.
- Baricitinib treatment was **safe** and well tolerated.
- These data support further testing of baricitinib in randomized clinical trials.

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The Journal of Clinical Investigation — CLINICAL MEDICINE

Baricitinib restrains the immune dysregulation in patients with severe COVID-19

Vincenzo Bronte,[1] Stefano Ugel,[1] Elisa Tinazzi,[2] Antonio Vella,[1] Francesco De Sanctis,[1] Stefania Canè,[1] Veronica Batani,[1] Rosalinda Trovato,[1] Alessandra Fiore,[1] Varvara Petrova,[1] Francesca Hofer,[1] Roza Maria Barouni,[1] Chiara Musiu,[1] Simone Caligola,[1] ...adello,[4] Simonetta Friso,[2] Francesca Pizzolo,[2] Manuela Iezzi,[5] ...tti,[7] Paolo Bazzoni,[7] Mariaelisa Rampudda,[7] Andrea Comel,[7]

...of Medicine, [3]Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University ...entistry, Maternity and Infant, University and Hospital Trust of Verona, Verona, Italy. [5]Center for Advanced Studies ...tment of Experimental Oncology, European Institute of Oncology (IEO), Istituto di Ricovero e Cura a Carattere

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M.K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. Oh, E.-S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L.A. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.-C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G.A. Deye, W. Dempsey, S.U. Nayak, L.E. Dodd, and J.H. Beigel,

NIH U.S. National Library of Medicine
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A Study of Baricitinib (LY3009104) in Participants With COVID-19 (COV-BARRIER)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Home > Search Results > Study Record Detail

Adaptive COVID-19 Treatment Trial 4 (ACTT-4)

Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study ★★,☆

Dear Editor,

As recently discussed in the Journal,[1] baricitinib was safe and improved the clinical conditions in 12 patients with mild-moderate Coronavirus Disease 2019 (COVID-19) pneumonia. It is known that severe symptoms of COVID-19 may develop after a median of 8-days from illness-onset, with a median time to Intensive Care Unit (ICU) admission of 5 days from the dyspnea occurrence.[2] Currently, no antiviral therapies or vaccines are available. An uncontrolled

teroids were not allowed. If patients were discharged earlier than 2 weeks, they were requested to continue the ongoing therapy until the scheduled 14-days.

Temperature, respiratory and pulse rate, arterial blood gas analysis, blood pressure, blood cell count, liver and kidney tests function were daily assessed. IL-6 serum levels of (RayBio® Human IL-6 ELISA Kit, RayBiotech Co.,USA) were tested at baseline, week 1 and 2. Since low lymphocyte percentage can predict a poor prognosis[6], patients were stratified at baseline as: lymphocytes >20%, >5% to <20%, and <5%.

Patients provided a written-informed consent. The off-label use of baricitinib was approved by the Hospital-Committee and