Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Secukinumab in severe COVID-19 pneumonia: Does it have a clinical impact?

Dear Editor,

The recently published meta-analysis[1] in the journal showed better treatment outcome with the short term use of tocilizumab, an interleukin (IL)-6 inhibitor, in patients with severe coronavirus disease 2019 (COVID-19) which was first reported as an Outbreak in Wuhan, China, in December 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Cytokine storm in severe COVID-19 is characterized by hyperactivity of proinflammatory cytokines, chemokines, and growth factors including IL-6, and tocilizumab down-regulates the overexpression of IL-6 by inhibiting IL-6 receptors resulting in suppression of cytokine storm.[2]

About one-third of SARS-CoV-2 infected hospitalized patients develops symptoms of severe COVID-19 pneumonia leading to acute respiratory distress syndrome and upon progression, results in respiratory failure.[3] To date, no standard anti-inflammatory drug therapy in COVID-19 has yet been recommended but, baricitinib, a Janus kinase (JAK)1 and 2 inhibitor recommended for the treatment of rheumatoid arthritis (RA), has been declared as an emergency medicine along with remdesivir, an anti-viral agent, for this purpose under the Emergency Use Authorization (EUA) of the U.S. Food and Drug Administration (FDA). Baricitinib 4 mg daily following an 8 mg of loading dose was found beneficial in moderate-severe COVID-19 pneumonia.[4]

Besides significant mortality benefit, tocilizumab was found with improved clinical outcome in severe COVID-19 pneumonia in several studies on different Ethnic groups worldwide[2,3] but, the use of this costly medicine in patients with severe COVID-19 becomes a huge treatment cost-burden specially for the people of low and middle-income countries.[5] Moreover, recent data suggest that inhibition of IL-6 is not the only way to down-regulate cytokine storm effectively in COVID-19, and there may be other potential pathways to substantially progress hyper-inflammatory responses in COVID-19 positive host body.[6]

In SARS-CoV-2 infection, several cytokines such as IL-6 and transforming growth factor β (TGF-β) via janus kinase (JAK)-2/Signal transducer and activator of transcription (STAT)-3 pathway potentiate the activation of CD4+ T cells exuberantly resulting in T-helper-17 (Th17) cells differentiation in host leading to excessive release of inflammatory cytokines, including IL-17A. Secukinumab is a recombinant human monoclonal immunoglobulin G1 (IgG1)/κ antibody that selectively inhibits IL-17A.[7] Evidence of using IL-17A inhibitor (secukinumab) as targeted therapy in COVID-19 pneumonia is rare but, nowadays secukinumab is at point-of-therapeutic interest in COVID-19.[7–9]

From 19 February 2021 to 30 March 2021, among the admitted patients with confirmed severe COVID-19 pneumonia at Square Hospitals Ltd., Dhaka, Bangladesh, 17 patients were (N) treated with secukinumab (Cosentyx; Novartis International AG, Basel, Switzerland) (300 mg intravenously, mixed with 100 mL of 0.9% Sodium chloride solution and administered over 1 h) (single dose) plus baricitinib (4 mg orally once daily for 14 days) considered as SNB-BCB group and another 17 patients (N) received only baricitinib (4 mg orally once daily for 14 days) therapy considered as BCB group. Remdesivir (200 mg loading at day 1, then 100 mg once daily for up to day 4), dexamethasone (0.25 mg/Kg of body weight; max: 20 mg/day), and anticoagulants were commonly used in all patients of both the groups. Antibiotics and antifungals were used in patients according to microbiological culture sensitivity test.

Inclusion criteria: (a) SARS-CoV2 is present in the nasal/oral swabs; (b) at least two of the following signs of severe COVID-19 pneumonia with confirmed pneumonia lesions (bilateral ground-glass opacities) (>50%) in the chest computed tomography (CT) scan images: (I) dyspnea; (II) oxygen saturation in peripheral blood (SpO_2) level ≤93% on room air; and (III) respiratory rate ≥30 breaths/min; and (c) Onset of symptom(s)-to-hospitalization no more than 10 days. Exclusion criteria: (a) history of any autoimmune disease, latent tuberculosis infection, and malignancy; (b) recent history of surgery or viral infections; and (c) pregnancy and lactation.

Severe COVID-19 pneumonia is characterized by oxygen saturation in peripheral blood (SpO_2) <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory rate >30 breaths/min, and lung infiltrates >50% in chest CT scan.[3] Patients' vital signs, hematological parameters, liver enzymes, infection markers, progression of COVID-19 pneumonia through radiological investigation (X-ray), and Modified Early Warning Score (MEWS) were evaluated daily by a board of medical experts.

This study was approved by the Research Ethics Committee of Square Hospitals Ltd, Dhaka, Bangladesh (no. 2901SH-OS02) on February 11, 2021. Written consent was taken from all participants in the study. The Statistical Product and Service Software (SPSS ver. 22.0, Chicago, IL, USA) was used in the study for statistical analysis of the data. Descriptive statistics were presented through median value with interquartile range (IQR). Continuous variables were compared using Student's *t*-test, and categorical variables were compared using Pearson Chi-square test. A *P* value ≤0.05 was considered statistically significant.

Seventeen patients (N) were enrolled in each group and the median age of the patients was 52 years/54 years (SNB-BCB/BCB group). Table 1 showed clinical manifestations of COVID-19 infec-

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Table 1
Baseline demographic information, symptoms of COVID-19, comorbidity and laboratory findings in patients treated with secukinumab plus baricitinib or baricitinib only.

Variable	SNB-BCB group ($N = 17$)	BCB group ($N = 17$)	P value
Male/female, *n* (%)	9/8 (53/47)	10/7 (59/41)	0.728
Age (year), median (IQR)	52 (45–58.5)	54 (44.5–61.5)	0.725
Onset of symptom-to-hospitalization time, median (IQR)	6 (4.5–7)	7 (6–8)	0.006
Onset of symptom-to-SNB therapy initiation time, median (IQR)	9 (8.5–11)	10 (9–11.5)	1.0
Fever (°F), median (IQR)	101 (99.5–101)	101 (99–102)	0.601
Dry cough, *n* (%)	16 (94.11)	14 (88.23)	1.0
Weakness, *n* (%)	12 (70.59)	15 (88.24)	0.398
Dyspnea, *n* (%)	15 (88.24)	11 (64.71)	0.225
Headache, *n* (%)	8 (47.06)	9 (52.94)	0.634
Anosmia, *n* (%)	14 (82.35)	15 (88.24)	1.0
Diarrhea, *n* (%)	10 (58.82)	12 (70.59)	0.636
Sore throat, *n* (%)	9 (52.94)	4 (23.53)	0.157
Diabetes, *n* (%)	12 (70.59)	8 (47.06)	0.296
Hypertension, *n* (%)	11 (64.71)	10 (58.82)	1.0
IHD, *n* (%)	3 (17.65)	4 (23.53)	1.0
Bronchial asthma, *n* (%)	3 (17.65)	1 (5.88)	1.0
CKD, *n* (%)	5 (29.41)	3 (17.65)	0.688
COPD, *n* (%)	1 (5.88)	2 (11.76)	1.0
Obesity, *n* (%)	6 (35.29)	5 (29.41)	0.438
PUD, *n* (%)	5 (29.41)	7 (41.18)	0.721
CLD, *n* (%)	2 (11.76)	3 (17.65)	1.0
PD, *n* (%)	2 (11.76)	1 (5.88)	1.0
SpO_2 (%), median (IQR)	90 (89–90)	90 (87.5–90)	0.369
PaO_2/FiO_2 (mmHg), median (IQR)	255 (211.5–284.5)	260 (200–287)	0.888
RSO, median (IQR)	7 (5–8.5)	8 (4–9.5)	0.691
Respiratory rate, (breaths/min), median (IQR)	25 (22–26)	25 (22.5–26)	0.748
Heart rate (beat/min), median (IQR)	100 (84.5–106)	87 (82–102)	0.172
CRP (mg/L), median (IQR)	174.7 (96.8–247.5)	120.3 (34.6–279.9)	0.453
Procalcitonin (ng/mL), median (IQR)	2.17 (1.06–4.74)	0.98 (0.08–1.29)	0.045
WBC (K/μL), median (IQR)	7.9 (5.11–11.55)	7.89 (5.92–11.9)	0.364
Neutrophils (%), median (IQR)	87.6 (79.05–94)	89.7 (82.15–90.5)	0.897
Lymphocytes (%), median (IQR)	11.9 (10.19–14.65)	12.9 (9.25–14.85)	0.787
Platelet (K/μL), median (IQR)	156 (105.5–197)	214 (99–313)	0.120
D-dimer (mg/L FEU), median (IQR)	4.71 (3.79–7.1)	5.4 (3.59–6.98)	0.377
IL-6 (pg/mL), median (IQR)	127(51–196)	122 (74.5–214)	0.761
Serum Ferritin (ng/mL), median (IQR)	631 (514.5–843)	631 (490–736.5)	0.528
LDH ((U/L), median (IQR)	549 (444–644.5)	476 (396.5–642)	0.738
Creatinine (mg/dL), median (IQR)	1.4 (1.25–2.1)	1 (0.65–1.25)	0.822
ALT (U/L), median (IQR)	57 (41.5–66.5)	58 (48–77.5)	0.151
AST (U/L), median (IQR)	35 (28.5–46.5)	38 (30.5–47.5)	0.815
MEWS, median (IQR)	2 (2–3)	2 (2–3)	0.734

Abbreviations and symbols: SNB = secukinumab; BCB = baricitinib; IQR = interquartile range; *n* = number; % = percentage;°F = grade Fahrenheit; IHD = ischemic heart disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PUD = peptic ulcer disease; CLD = chronic liver disease; PD = parkinson's disease; SpO_2 = oxygen saturation in peripheral blood; PaO2/FiO2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen; mmHg = millimeter of mercury; RSO = requirement of supplemental oxygen; min = minute; CRP = C-reactive protein; mg = milligram; L = liter; FEU = fibrinogen equivalent units; ng = nanogram; WBC = white blood cells; K/μL = thousand cells per micro liter; IL = interleukin; pg/mL = picograms per milliliter; LDH = lactate dehydrogenase; U/L = units per liter; dL = deciliter; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MEWS = Modified Early Warning Score.

tion, comorbidities, infection markers, hematological parameters, hepatic functions, and MEWS of all patients of the study.

Baricitinib-associated elevation of platelet count (636 K/μL of blood) in BCB group was the only adverse event found in the study.

Table 2 illustrated the comparison of clinical outcomes between the two groups. Compared to patients in BCB group, patients in SNB-BCB group showed more normal breathing function within 48 h of therapy initiation ($P = 0.180$); less requirement of ICU and intubation support ($P < 0.05$), shorter length-of-ICU stay ($P = 0.042$), and less 30-day mortality rate ($P = 0.033$). In contrary, secondary infections were higher in patients of SNB-BCB group (17.65%/5.88%, respectively, $P > 0.05$).

All the comparisons mentioned above demonstrates that addition of a single intravenous 300 mg dose of secukinumab to 4 mg daily oral baricitinib for 14 days improves clinical outcomes, including normalization of breathing function, severity of the disease and survival, and reduce the risk of ICU and invasive mechanical ventilation support.

Open-label comparative study design with small sample size was the major limitation of the study.

Thus, secukinumab plus baricitinib may reduce the severity of cytokine storm in severe COVID-19 which may ultimately improve clinical outcomes and survival in patients with severe COVID-19 pneumonia.

Declaration of Competing Interest

None.

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Table 2
Clinical outcomes in patients with severe COVID-19 pneumonia treated with secukinumab plus baricitinib or baricitinib only.

Parameters	SNB-BCB group ($N = 17$)	BCB group ($N = 17$)	P value
Patients achieved normal breathing functions within 48 h, *n* (%)	11 (64.71)	7 (41.18)	0.180
Patients achieved normal breathing functions[a] within 96 h, *n* (%)	2 (11.76)	1 (5.88)	0.559
ICU support required, *n* (%)	4 (23.53)	9 (52.94)	0.020
HFNC oxygen therapy required, *n* (%)	2 (11.76)	4 (23.53)	0.384
Intubation required, *n* (%)	2 (11.76)	5 (29.41)	0.011
Secondary infections			
Bacterial (lower respiratory tract)	3 ($2^b + 1^c$) (17.65)	1^b (5.88)	0.601
Fungal (upper respiratory tract)	2^d (11.76)	0	1.0
Length-of-hospital stay (day), median (IQR)	12 (11.25–14)	19 (16–23.75)	0.042
30-day all-cause mortality, n (%)	1 (5.88)	3 (17.65)	0.033

Abbreviations and symbols: a = SpO_2 ≥94% on room air; b = gram-negative bacterial infection; c = gram-positive bacterial infection; d = *Candida albicans* infection; HD = high dose; UD = usual dose; SpO_2 = peripheral capillary oxygen saturation; IQR = interquartile range; ICU = intensive care unit; HFNC = High-flow nasal cannula; *n* = number; % = percentage.

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References

1. Tharmarajah E, Buazon A, Patel V, Hannah JR, Adas M, Allen VB, et al. IL-6 inhibition in the treatment of COVID-19: a meta-analysis and meta-regression. *J Infect* 2021;**82**(5):178–85. doi:10.1016/j.jinf.2021.03.008.
2. Pelaia C, Calabrese C, Garofalo E, Bruni A, Vatrella A, Pelaia G. Therapeutic role of tocilizumab in SARS-CoV-2-induced cytokine storm: rationale and current evidence. *Int J Mol Sci* 2021;**22**(6):3059. doi:10.3390/ijms22063059.
3. Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoğlu U. Severe covid-19 pneumonia: pathogenesis and clinical management. *BMJ* 2021;**372**:n436. doi:10.1136/bmj.n436.
4. Hasan MJ, Rabbani R, Anam AM, Huq SMR. Additional baricitinib loading dose improves clinical outcome in COVID-19. *Open Med* 2020;**16**(1):41–6. doi:10.1515/med-2021-0010.
5. Hasan M J. Tocilizumab in COVID-19 treatment: a cost-burden in low- and middle-income countries. *Int J Health Life Sci* 2000;**6**(2):e104480. doi:10.5812/ijhls.104480.
6. Du P, Geng J, Wang F, Chen X, Huang Z, Wang Y. Role of IL-6 inhibitor in treatment of COVID-19-related cytokine release syndrome. *Int J Med Sci* 2021;**18**(6):1356–62. doi:10.7150/ijms.53564.
7. Shibabaw T. Inflammatory cytokine: IL-17A signaling pathway in patients present with COVID-19 and current treatment strategy. *J Inflamm Res* 2020;**13**:673–80. doi:10.2147/JIR.S278335.
8. Mendoza VMM. Interleukin-17: a potential therapeutic target in COVID-19. *J Infect* 2020;**81**(2):e136–8. doi:10.1016/j.jinf.2020.05.072.
9. Coskun Benlidayi I, Kurtaran B, Tirasci E, Guzel R. Coronavirus disease 2019 (COVID-19) in a patient with ankylosing spondylitis treated with secukinumab: a case-based review. *Rheumatol Int* 2020;**40**(10):1707–16. doi:10.1007/s00296-020-04635-z.

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