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SHORT COMMUNICATION

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Compassionate Use of Opaganib for Patients with Severe COVID-19

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Abstract

Opaganib is a Sphingosine-kinase (SK)-2 inhibitor with anti-inflammatory and anti-viral properties. Five severe COVID-19 patients were treated with opaganib on compassionate-use basis. Treatment was well tolerated and associated with faster lymphocyte count increase and improved oxygenation. Opaganib efficacy for COVID-19 should be examined in a clinical trial setting.

Keywords: COVID-19; Opaganib; Compassionate-use

Introduction

Opaganib (RedHill Biopharma Ltd.) is a selective SK-2 inhibitor with anti-inflammatory and anti-viral properties. Sphingomyelin is the precursor of ceramide and the proinflammatory lipid sphingosine 1-phosphate (S1P). Increasing intracellular S1P levels and depletion of ceramide promote cell proliferation and inhibit apoptosis. Platelets, monocytes, and mast cells secrete S1P upon activation, thus promoting inflammatory cascades [1,2]. Moreover, SK activation is essential for the signaling responses to Tumor Necrosis Factor alpha [3]. Opaganib (ABC294640) is an orally available SK-2 inhibitor noted to have anti-inflammatory activity in rodent models of arthritis and inflammatory bowel disease [4-6] as well as anti-viral effects. Impairment of SK-2 function significantly inhibited Chikungunya virus infection [7], decreased viral titers of Influenza in an in-vitro model [8] and demonstrated inhibitory effect in Ebola cell-based inhibition assay [9].

Three clinical trials have been completed with opaganib, a phase 1 study in advanced solid tumor patients [10], a food effect study in healthy volunteers and a phase 1b/2 in patients with advanced multiple myeloma (unpublished). Two more studies are in progress, a phase 2 study in advanced prostate cancer (clinicaltrials.gov ID: NCT04207255) and phase 2 study in cholangiocarcinoma (clinicaltrials.gov ID: NCT03377179).

Here we report our experience with this treatment in COVID-19 patients and compare patients' outcomes to those of untreated patients with similar disease severity.

The Study

Shaare-Zedek Medical Center (SZMC) is a tertiary academic hospital in Jerusalem, IL. On February 27th the first case of COVID-19 was diagnosed in Israel, with a dramatic increase in the number of cases following a Jewish holiday in the middle of March. Many cases were diagnosed in the orthodox Jewish communities of Jerusalem, which the hospital serves.

RedHill Biopharma, Ltd. offered opaganib under compassionate use for the treatment of COVID-19 patients. Eligible patients were those hospitalized with severe COVID-19, requiring oxygen support *via* high-flow nasal cannula (HFNC). Intubated or debilitated patients, pregnant or nursing women, patients on oral anti-coagulants or evidence of ischemia on ECG were excluded. In addition to signing the informed consent, patients were required to have acceptable liver and renal function. Oral opaganib was delivered at a dose of 500 mg q12 hours for up to 14 days, or until patient discharge. Additional therapy was allowed as deemed necessary by the clinicians. Data were collected through May 5, 2020.

Assessment and analysis

Clinical data were collected daily until patient discharge. For comparison, we used a control group with same-sex, same-severity (male patients requiring HFNC oxygen support), aged 35 to 80 years, who met the inclusion and exclusion criteria. These patients may have been eligible for treatment, but were not approached due to time and staff constraints.

Ethical considerations

Individual approval was granted for each patient treated with opaganib by the SZMC institutional review board (IRB) and the Israeli Ministry of Health. Written informed consent was obtained from each participant. For the control group, IRB approval was granted to collect de-identified data. RedHill Biopharma Ltd. provided the medication, but was not involved in the conduct of treatment or follow-up, nor in the data collection and analyses.

Univariate comparisons between the groups were performed with chi-square test for categorical variables and t-test or Mann-Whitney U-test for continuous variables, as appropriate. Time variables were compared with Cox proportional hazard regression, adjusted for age and background illnesses. C-reactive protein (CRP) and lymphocyte counts were recorded at day 1 (treatment or admission) and at interval of 2-4 days, and compared with repeated measures general linear model with Bonferroni correction for multiple comparisons. All analyses were conducted with SPSS software, version 25.0 (IBM).

Seven patients received at least one dose of opaganib since April 2, 2020. All patients received Hydroxychloroquine (HCQ), however one stopped HCQ prior to opaganib treatment due to borderline Q-T interval in ECG. Three patients received azithromycin as well. One patient, who received both HCQ and azithromycin, developed diarrhea after two doses of opaganib, and the treating physicians decided to stop all his medications. A second patient was discharged after receiving two doses of opaganib. Therefore, five patients were included in this analysis. Overall, 3 received the full 14-day course of opaganib, and 2 patients received 11 and 7 days respectively, before being discharged. All patients who received opaganib were male (as approximately two-thirds of severe patients in SZMC).

Safety

Except for diarrhea in one patient, no other adverse events related to the medication were observed. One patient reported dysuria on day 12 of treatment and another patient had an episode of atrial fibrillation that resolved spontaneously.

Baseline characteristics

Median age, rates of diabetes, hypertension and obesity, as well as median duration of symptoms prior to admission were similar between treatment and control groups (Table 1). Cases had somewhat higher baseline lymphocyte counts and lower D-dimer levels compared with controls. All patients received HCQ, and the majority also received azithromycin. However, methylprednisolone was given to a third of controls and to none of cases.

Clinical and laboratory outcomes

Lymphocyte counts increased significantly faster in the treatment group (p=0.001, Figure 1). Of note, a third of the control patients received systemic steroids. In order to exclude bias related to the lymphocytopenic effect of steroids, the general linear model was performed again excluding these 6 patients, yielding similar results (p=0.013).

All other outcomes trended in favor of the opaganib group , however did not reach statistical significance: CRP decreased faster among cases (p=0.08, Figure 2) , median time to weaning from HFNC (time to NC) was 10 days (IQR: 9-15.5) compared with 15 days (IQR: 8-19) in cases vs. controls [Hazard ratio (HR)=0.3, 95% CI: 0.07-1.7, p=0.2] and time to breathing ambient air was 13 days in the opaganib group (IQR: 10.5-19) *vs.* 14.5 days in the controls (IQR: 10-28); (HR=0.4, 95% CI: 0.15-1.5).

Table 1: Baseline characteristics of the patients*.

Characteristic	Opaganib (N=5)	Control (N=18)	*p*
Median age (IQR*), Years	58 (50-73.2)	58.5 (54.5-66)	0.9
Median duration of symptoms before admission (IQR), days	7 (6-8)	6 (2.5-8)	0.5
Coexisting conditions-no.(%)			
Hypertension	2 (40)	6 (33)	1
Diabetes Mellitus	2 (40)	6 (33)	
Obesity	2 (40)	8 (44)	
Baseline laboratory values, Median (IQR)			
CRP, mg/dL	15.8 (12.6-21.7)	18.6 (9-26.7)	0.6
Lymphocytes, mm^3	1100 (995-1300)	850 (635-970)	0.09
Fibrinogen, mg/dL	858 (844-2746)	741 (676-828)	0.04
D-dimer, ng/mL	1208 (531-2633)	1578 (1073-3734)	0.07
Ferritin, ng/mL	1483 (999-5180)	758 (530-1109)	0.3
Concomitant medications given for COVID-19, N (%)			
Hydroxychloroquine	5 (100)	18 (100)	1
Azithromycin	3 (60)	14 (77)	0.5
Methylprednisolone	0	6 (33)	0.2
Cycle threshold (Ct) value In RT-PCR of nasal swabs**	24.8 ± 2.6	25.9 ± 5.5	0.8

*All patients are male; IQR-Interquartile range
**Values of cycle threshold are an average of E, N and RdRp genes tested

Complications

All patients in the treatment group were discharged by the time of data collection; none have required mechanical ventilation or suffered complications. Among controls, 5(27%) patients were not discharged by the time of data collection, 6 (33%) required mechanical ventilation (p value compared with opaganib group=0.13), 2 (11%) required ECMO, and 1 required tracheostomy. None of the patients in both groups had died by the time of data collection.

Conclusions

At the time of this study, no effective treatment was available for COVID-19 infection. Only at the end of this data collection, a preliminary report was published which showed some improvement in clinical outcomes of severe COVID-19 patients treated with remdesivir [11]. Neither remdesivir nor other potential treatments such as convalescent plasma, were available for our patients. The anti-inflammatory and anti-viral properties of opaganib along with a good safety profile motivated us to offer it under compassionate use to severe COVID-19 patients.

Patients treated with opaganib had significantly faster increase in lymphocyte count. Low lymphocyte counts were associated with a more severe COVID-19 disease [12] and with faster disease progression [13,14]; therefore this faster increase may indicate better prognosis for the treatment group. Interestingly, the faster lymphocyte

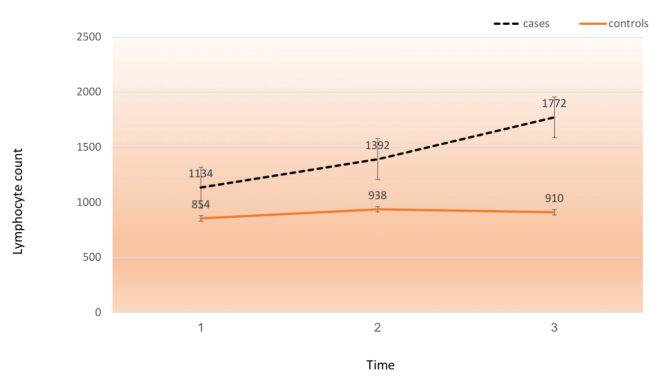

Figure 1: Lymphocytes (counts/mm^3) increase in cases (dashed line) *vs.* controls (solid line) over three time points (day of admission or day of treatment start and every 2-4 days), p=0.001.

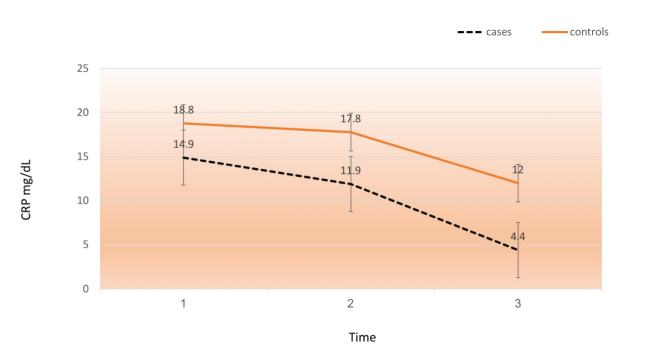

Figure 2: C-reactive protein (mg/dL) decrease in opaganib treatment (dashed line) *vs.* controls (solid line), over three time points (day of admission or day of treatment start and every 2-4 days), p=0.08.

recovery among opaganib treated patients persisted even after excluding control patients who received systemic steroids. Although other clinical outcomes did not differ significantly between groups, the trends of time to improved oxygenation, rate of CRP decrease, as well as rates of mechanical ventilation and complications were all in favor of the treatment group.

Opaganib treatment was well tolerated. Only in one patient was treatment stopped, due to diarrhea, while being treated with HCQ and azithromycin in addition to opaganib.

The results of the present report are preliminary and are limited by the small number of patients. However, these data justify examining the effect of opaganib in the setting of a clinical trial, with larger numbers of patients and, potentially, with moderate disease severity.

Conflict of Interest Statement

All authors declare no conflict of interest.

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