Nelfinavir for COVID19: Summary of basic science data and initial clinical experience

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Case Report

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Abstract

Based on in vitro and computational model data that nelfinavir is highly active again SARS-CoV-2, we administered nelfinavir to six COVID-19 outpatients. Three of four acute outpatient COVID-19 patients became afebrile within 48 hours. In contrast, the two subacute COVID-19 patients with predominant GI symptoms responded only partially to nelfinavir.

Background

Despite initial excitement for hydroxychloroquine as a treatment for COVID-19 (1,2), emerging evidence dampened initial excitement (3–5). While studies for inpatients demonstrated that remdesivir can shorten hospitalization by 4 days, (6) there are no proven treatment for outpatients.

Because none of the clinical trials to date provided us with useful outpatient treatment, we returned to basic science reports looking for a practical interim solution. Nelfinavir is an oral antiretroviral protease inhibitor used in the therapy and prevention of human immunodeficiency virus. In vitro data from multiple groups have shown that nelfinavir has activity against SARS-CoV-2 (7,8). Research team from National Institute of Infectious Disease of Japan found that nelfinavir is the most potent protease inhibitor against SARS-CoV-2, 3-5 times more potent than lopinavir/ritonavir (9). Several computational models also confirmed that nelfinavir can bind SARS-CoV-2 main protease (Mpro) at the Glu166 position (7,8), and this interaction is quantitatively greater than that of lopinavir and ritonavir (10). Furthermore, a more recent computational model suggested that nelfinavir can also attack the SARS-CoV-2 Spike protein, inhibiting viral entry into the cell (8).

We here report the initial experience of the application of nelfinavir on six outpatients in New York City in April 2020.

Case Reports

1) 4 patients with fever and predominantly respiratory involvement and symptoms of less than 14 days-> 3 out of 4 patients became afebrile and symptomatically better within 48 hours of nelfinavir and most symptoms resolved by day 4.

a. First Case: A previously healthy 50-year old woman developed cough, fever up to 103 F degrees, diarrhea and myalgia. On Day 6 she was initially treated with azithromycin. RT-PCR for SARS-CoV-2 was negative. On Day 10, her cough and shortness of breath worsened significantly, and she was started on nelfinavir 1250 mg two time a day (and one dose of 80 mg baloxavir). But due to severe dyspnea, she went to emergency room. CXR showed right lower infiltrate. Oxygenation saturation on room air was 92-94%. CBC was abnormal only for low lymphocyte count (=0.6 10*3/uL). ALT =246 u/L. D-dimer normal. Troponin=0.04 ng/ml. Due to overcrowding of emergency room, she was discharged home after 3 hours, still very symptomatic. Fortunately, 48 hours after nelfinavir initiation, she became afebrile. 4 days after administration of nelfinavir, all of her symptoms resolved except for mild cough and mild diarrhea. Mild diarrhea remained until day 7 post nelfinavir She completed 14 days of nelfinavir with no recurrence of symptoms or diarrhea.

b. Second Case: 65-year old man with history of COPD and hypertension, presented with fever 102 F degree, cough, and oxygenation saturation 92-94%. RT-PCR for SARS-CoV-2 was positive. He was initially started on hydroxychloroquine for five days and one dose of baloxavir with no response. Approximately one week after the onset of his symptom, he was started on nelfinavir 1250 mg two times a day. 48 hours post Nelfinavir, his cough and fever resolved. Mild diarrhea persisted until the end of the 14-day nelfinavir course.
c. Third Case: 55-year old man presented with one day of fever of 103 F, sore throat and cough after close contact with a confirmed COVID-19 patient. Past history and medication included the use of losartan and atorvastatin for hypertension and hyperlipidemia. He was started on nelfinavir 1250 mg two times a day. He became afebrile in 48 hours, but spiked fever again after 72 hours. 80 mg baloxavir was added. He became afebrile and asymptomatic day 7 post onset of symptoms. No diarrhea developed
d. Fourth case: 45-year old woman with diabetes presented with fever and malaise, RT-PCR COVID-19 positive. She was initially treated with one dose of baloxavir and hydroxychloroquine for 5 days. Three days after completion of the course, her fever subsided, but severe headache, malaise and myalgia continued. She was started on nelfinavir 1250 mg two times a day, and 48 hours after initiation, all the symptoms resolved. No diarrhea developed.

2) 2 patients with subacute presentation (onset > 21 days) with predominant GI symptoms (abdominal pain and diarrhea) without fever: the response to nelfinavir was partial and delayed.

a. First Case: 30-year old woman, with no past history, RT-PCR SAR-CoV-2 negative, with subjective fever and chill, diarrhea and cough 23 days prior to first dose of nelfinavir. Despite initial treatment on hydroxychloroquine and baloxavir, chill and diarrhea persisted. She was started on nelfinavir, but worsening diarrhea resulted in dehydration and nelfinavir was stopped after four days.
b. Second Case: 30-year old woman, COVID-19 contact, with persistent subjective fever, 3 times per day diarrhea, and abdominal pain despite treatment with hydroxychloroquine and azithromycin. 30 days after onset of symptoms, she was started on nelfinavir and baloxavir: after 8 days of treatment, diarrhea disappeared, but she continued to have mild chill and only partial relief of her abdominal pain.

Discussion

We found that after in three of four acute outpatient COVID-19 patients became afebrile within 48 hours; the empiric addition of baloxavir to nelfinavir may have been helpful. In contrast, the two subacute COVID-19 patients with predominant GI symptoms only responded partially to nelfinavir.

At time of writing (May 3, 2020), the NIH guideline states that “except in the context of a clinical trial, the COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of the following drugs for the treatment of COVID-19: Lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII) because of unfavorable pharmacodynamics and negative clinical trial data.”(11). Similarly, NEJM has commented that “for the Covid-19 pandemic and other pressing medical challenges, the health of individual patients and the public at large will be best served by remaining true to our time-tested approach to clinical trial evidence and drug evaluation, rather than cutting corners and resorting to appealing yet risky quick fixes.” (12) The NIH guideline on antiviral is based on the negative clinical study of lopinavir–ritonavir (13), which is much less potent than nelfinavir. But

the fact remains for the frontline physicians that five months into the pandemic, we do not have an effective treatment for outpatient COVID-19 patients.

Based on in vitro antiviral activities and computational data, nelfinavir is among the strongest anti-SARS-CoV-2 candidate among medications easily accessible to North American physicians. While the anti-parasitic drug ivermectin, has also shown in vitro activity and has garnered media interest(14), the blood level required to kill the virus far exceed possible with dosage being used clinically.(15) In contrast, nelfinavir drug level in plasma, mononuclear cells, and lung achieved is significantly higher than the level required to kill the virus in vitro.(7)

In computer modeling by Japan National Institute of Infectious Disease, nelfinavir is predicted to decrease duration of illness by 4 days based on in vitro data (16) , similar to the decrease of hospitalization days seen with remdesivir. (6) In our cohort, three of four acute cases responded similarly to the response to the first US COVID-19 patient after remdesivir intravenous injection: fever and oxygenation saturation stabilized shortly after administration, while cough lasted longer. In contrast to the favorable response in our acute patients in our cohort, the two subacute patients with predominant GI symptoms had only partial effect to nelfinavir. GI involvement in COVID-19 is increasingly recognized. (17,18) The pathophysiology of COVID-19 GI tract involvement may be complex: in HIV enteropathy which has similar clinical presentation, GI tract continues to suffer from chronic inflammation and intestinal barrier dysfunction despite antiviral therapies (19,20). Prolonged antiviral therapies and additional therapies may be required to adequately address this problem.

Prior to our report, the media reported one successful case using nelfinavir in Shanghai in January 2020 (21). However, the drug has not been tested clinically in Europe and China because marketing authorization for nelfinavir has not been renewed in EU and in China by the pharmaceutical company(22,23). In US and Canada, despite being off patent, nelfinavir is only manufactured by one manufacturer with no generic options. The drug is not covered by many medical insurance plans and is approximately $700 per 2-week course. Nelfinavir can cause diarrhea in about 20% of HIV patients, and calcium carbonate was found to be helpful (24). Among our cohort, nelfinavir triggered or worsened diarrhea in two patients while it helped COVID-19 related diarrhea in two patients. Calcium carbonate, which has been recommended as a treatment of HIV nelfinavir-induced diarrhea, only had minimal effect for nelfinavir-induced diarrhea in our COVID-19 cohort. Aside from mild diarrhea and drug interaction, it is generally well tolerated; no dose adjustment is needed for renal failure and mild liver impairment. (25)

Baloxavir marboxil is an inhibitor of influenza virus cap-dependent endonuclease and has not been proven to be effective in COVID-19 (26). Many local practitioners have been using baloxavir for COVID-19 in our community, and we have decided to include the medication in the regimen for potential adjunctive effect.

If this encouraging experience is confirmed in clinical trial, nelfinavir will provide outpatient physicians an oral antiviral that can prevent patient hospitalization, especially for the patients with symptoms for less than two weeks. Like oseltamivir for influenza, nelfinavir may need to be given early to have maximal therapeutic effect.

Declarations

Ethics approval and consent to participate: Not applicable. This is a retrospective case series.

Consent for publication: all patients in the case report have given consent to this report

Availability of data and material: not applicable

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