

Commentary

Potential Interventions for SARS-CoV-2 Infections: Zinc Showing Promise

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In the early weeks of the COVID-19 pandemic, Zang and Yunhui discussed in the Journal of Medical Virology various treatment approaches as potential interventions against the virus including zinc (Zn)¹. In the six months since that publication, information has emerged that Zn may be important for natural protection against SARS-CoV-2 severity, as well as an effective tool for treatment.

Intracellular elemental zinc (Zn) inhibits various RNA viruses including coronaviruses². In a 2010 study, Zn coupled with an Zn ionophore (pyrithione), showed potent inhibition of SARS-CoV replication (even at very low micromolar concentrations). Zn directly inhibited the coronaviral RNA-dependent RNA polymerase, which functions as the core enzyme of the RNA viral synthesizing machinery². Zn also inhibits SARS-CoV papain-like protease 2 (PLP2), which is also a key enzyme for viral replication and assembly of functional viral proteins³. Zn and several Zn chelates were shown to inhibit furin (proprotein convertase) which is important in the pathogenesis of many viruses⁴. The furin proteases have been proposed as therapeutic targets for several viral pathogens⁵. Specifically, the spike glycoprotein of SARS-CoV-2 contains a unique furin cleavage site that is not found in SARS-CoV⁶. This furin activation mechanism increases the infectivity and pathogenicity of viruses⁶. Zn inhibition of host furin in SARS-CoV-2 infection may be an important antiviral mechanism unique to this novel strain.

Chloroquine (CQ) has been shown to be a potent Zn ionophore and transports Zn through the cell membrane substantially increasing intracellular levels of Zn, especially in the endosomal-lysosomal compartment⁷. These same ionophore properties presumably apply to the closely related molecule, hydroxychloroquine (HCQ). Interestingly, coronaviruses enter cells via lysosomes / endosomes which requires proteolysis⁸.

There are other important mechanisms of Zn activity for viruses, likely including SARS-CoV-2: anti-inflammatory and/or immune modulation, altered receptor binding and expression (e.g. ACE2), among others^{9,10}.

Zn is not stored in the body, thus, must be obtained through the diet or supplements. The adult RDA for elemental Zn is 11 mg per day¹¹. Zn has been shown to be an important factor in respiratory viral pathogenesis / infections and Zn has been widely studied as a treatment for viral URIs^{9,10}. Global prevalence of Zn deficiency may be as high as 20%⁹. Zn deficiency has been demonstrated in diabetics and with increasing age^{10,12}. It has been estimated that 35% to 45% of adults ≥ 60 years have Zn intakes below the estimated average requirement¹². Almost 60% of elderly and nursing home residents in the U.S. showed decreased Zn intake levels¹⁰. Additionally, antihypertensive medications can increase urinary excretion of Zn^{10,12}. These conditions, associated with lower Zn levels, are now well recognized risk factors for severity of COVID-19 infection¹⁰.

Persistent low Zn levels have been found in critically ill patients and is associated with recurrent sepsis¹³. It is not clear as to whether the low levels were present before sepsis or was part of the acute illness. Either way, given that Zn has multiple roles in the defenses against COVID-19, such low levels are likely to be present in severe, critically ill COVID-19 patients. This could contribute to slow clearance of the virus and the severity of the illness. Thus, it is postulated that Zn deficiency may pose a risk factor for COVID-19 severity¹².

For Zn supplementation or treatment, several Zn compounds are available, mainly Zn salts. The amount of elemental Zn in these supplements ranges from 15% to 30%. An informal survey of common retail pharmacies by one of the authors, showed that Zn gluconate was the most common form sold (several different brands). These Zn salts, including Zn gluconate, usually list the amount of Zn as milligrams of elemental Zn and percent of RDA. As an example, Zn gluconate is often available as 50 mg of elemental Zn. Zn gluconate and Zn sulfate (discussed in the studies below) are well absorbed and recommended by the WHO to treat Zn loss from diarrhea¹⁴.

A study of hospitalized COVID-19 patients analyzed Zn as an add-on therapy to HCQ-azithromycin (AZ) combination¹⁵. HCQ dosing was 400 mg on day one and then 200 mg BID for 5 days. The Zn used was zinc sulfate, 220 mg (50 mg of elemental Zn) po BID, also for 5 days. They found an increased frequency of being discharged home (OR 1.5, 95% CI 1.12-2.09, $p<0.008$) and reduction in mortality or transfer to hospice (OR 0.449, 95% CI 0.271-0.744, $p<0.002$) in those patients (non-ICU) who received Zn add-on compared to those that did not receive Zn.

A study using a combination of Zn, low-dose HCQ and AZ for treatment of COVID-19 in outpatients also showed promising results¹⁶. The doses were: zinc sulfate 220 mg once daily, HCQ 200 mg BID and AZ 500 mg daily, all for 5 days. This study compared 141 risk-stratified COVID-19 patients (from a larger pool of all COVID-19 positives in the practice) treated with the triple regimen compared to 377 confirmed COVID-19 patients from the same community (other practices) that were used as untreated controls. Risk-stratified patients that met the criteria for treatment included: (A) age > 60 years, with or without symptoms; (B) age < 60 with shortness of breath; (C) age < 60 with at least one of several comorbidities. Median time between symptom onset and consultation was 4 days. Of the treated patients, 4 of 141 (2.8%) were hospitalized compared to 58 of 377 (15.4%) of the untreated patients (OR 0.16, 95% CI 0.06-0.5, $p<0.001$). In terms of mortality, one patient (0.7%) in the treated group died versus 13 (3.5%) in the untreated group (OR 0.2, 95% CI 0.03-1.5, $p=0.16$). Thus, there was an 84% reduction in hospitalizations and 80% decrease in mortality. Nausea and diarrhea were reported in 14% and 11%, respectively. No cardiac adverse effects were noted.

A key antiviral mechanism for these triple combinations may be the Zn inhibition of the SARS-CoV-2 virus. HCQ likely acts as a potent Zn ionophore.

There are other Zn ionophores available as dietary supplements. Examples are quercetin and epigallocatechin-gallate (ECGC), both bioflavonoids, which have been shown to be Zn ionophores¹⁷.

Zn, in the presence of a Zn ionophore (such as HCQ), shows potent anti-viral activity *in vitro* against coronaviruses such as SARS-CoV. This activity likely extends to SARS-CoV-2 and may potentially involve at least three different antiviral mechanisms discussed above. Zn deficiency may be associated with COVID-19 severity during infection and increase the risk of severity when present before infection. Maintaining normal Zn levels may help prevent illness severity in COVID-19 infection. An additional mechanism of HCQ activity in COVID-19 patients may be the Zn ionophore effect. Supplemental Zn has been shown to act together with HCQ (presumably acting as a Zn ionophore) in clinical studies of COVID-19 patients: demonstrating decrease hospitalizations, increased discharge in treated inpatients and decreased mortality. The elemental

Zn dose in these studies was 50 – 100 mg per day (as Zn sulfate). Zn should be considered as an add-on to HCQ treatment regimens (at least 50mg elemental Zn equivalent, based on above studies). Zn could potentially allow for short courses and low doses of HCQ, yet remain a highly effective regimen. As demonstrated in the treatment studies above, early therapy (outpatients) should be a target population. However, there was substantial benefit in hospitalized patients, especially if not severe enough to be in the ICU. Since Zn has shown these promising results with treatment of SARS-CoV-2 infection, it is tempting to speculate that Zn could be used for prophylaxis, particularly when paired with an ionophore such as HCQ. Other Zn ionophores, such as quercetin or ECGC, may have a role in early treatment and / or prophylaxis, when coupled with Zn. These combinations have not been studied thus far.

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