Research Article

Miglustat: A glycotransferase inhibitor for Covid-19 treatment

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) undergoes blood type specific glycosylation which has implications for infection susceptibility and replication without detection from the immune system. SARS-CoV-2 hijacks the host cell glycotransferase resulting in spike protein glycosylation resembling blood type antigens. Infection risk correlates to blood types that do not have anti-A and/or anti-B antibodies similar to that seen for ABO blood type recipients. The universal recipient AB is highly susceptible to infection lacking both anti-A and B antibodies, whereas blood type O has both antibodies resulting in less risk of infection. Once infected, SARS-CoV-2 obtains the blood type specific glycosylation of the host resulting in an effective camouflage against immune system recognition. Decoding the link between blood type and coronavirus disease 2019 (COVID-19) susceptibility exposes a role for miglustat a glycosyltransferase inhibitor in treatment. Use of the FDA-approved glycosyltransferase inhibitor miglustat can inhibit spike protein glycosylation revealing the SARS-CoV-2 virus for immune system recognition.

Title

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein is the main protein used in many vaccines, revealing its importance in immune system recognition of the SARS-CoV-2 virus. A recent paper by Grant et. al. showed the SARS-CoV-2 spike protein surface is highly shielded by glycans preventing antibody recognition.[1] Since the virus hijacks the host cellular machinery, spike protein glycosylation would obtain a host blood type glycan surface. As mentioned

by Grant et al the viral glycan shield may be composed of familiar host glycans.[1] Another study dealing with SARS-CoV-1 has indicated glycotransferase activity resulting in A antigen variant of the ABO blood group with anti-A antibodies able to cause virus neutralization.[2] Infection susceptibility may therefore be related to the ABO blood type recipients, and once infected the SARS-CoV-2 would obtain the host cell glycosylated coat becoming blood type specific.

The ABO blood-type is determined by the type of glycosylation found on the surface of red blood cells. The enzymes responsible for blood type glycosylation are known as glycotransferases.[2] There are four possible blood types A, B, O and AB while the Rh system is either Rh positive or negative.[3] Blood-typing identifies individuals who are recipients and/or donors of red blood cells. Blood type recipients lack antibodies to donor red blood cells with AB+ known as universal recipients.[3] While donors lack either A and or B surface antigens glycosylation making O- individuals known as universal donors.[3] The relationship to blood type and covid-19 has been demonstrated by many papers with blood type O found to have a decreased risk of morbidity and mortality associated with coronavirus disease 2019 (Covid-19)[4,5,6]. The impact of glycosylation on the ability of antibodies to bind the SARS-CoV-2 spike protein plays a role not only in infection susceptibility but also in replication without detection by the immune system.

In this paper a new antiviral mechanism of action is proposed for miglustat that is different from inhibition of receptor binding.[7,8] A main feature of SARS-Cov-2 is the avoidance of immune recognition by the protective glycan coat.[1] The mechanism of action purpose in this paper of miglustat is treatment of SAR-CoV-2 by the removal of the protective glycan coat exposing the virus to immune system recognition (Figure 1). Miglustat is a FDA approved drug for the treatment of Gaucher disease and Niemann-Pick disease type C because of its alpha-glucosidase inhibition.[9] Miglustat was shown to decrease the intracellular accumulation of glycosylcereride the glycolipid that accumulates in Gaucher disease. Side-effects with miglustat are common and included diarrhea, weight loss, gastrointestinal upset, nausea and vomiting, anorexia, constipation, headache, tremor, dizziness, paresthesia, peripheral neuropathy, ataxia, visual problems, and memory loss.[9] Side-effects are manageable since treatment duration with miglustat may be between 3-10days to correlate with the viral replication window.

DISCUSSION

The relationship of blood type susceptibility to SARS-CoV-2 infection is a result of host cell blood type glycosylation of the virus.[4,5,6] The SARS-CoV-2 spike protein obtains a similar glycan coat as red blood cells, and infection susceptibility becomes related to blood type recipients. An AB blood type is universally susceptible to SARS-CoV-2 similar to the universal recipient status of AB whereas blood type O has less risk of infection. Reports have shown blood groups A or AB are at increased risk from SARS-CoV-2 infection versus those of blood group O an B.[4,5,6] These results correlated with those seen in table 1 where AB and A have 100% to 88% susceptibility respectively to SARS-CoV-2, whereas blood-type B and O are less susceptible with 55% and 46%, respectively. The anti-A and anti-B antibodies of blood type O individuals provide a barrier to infection from A, B, and AB blood type individuals infected with SARS-CoV-2. However, blood type O individuals can become infected by SARS-CoV-2 infected blood type O individuals. Once an individual is infected by SARS-CoV-2 they produce viruses with glycans matching the host blood type. The spike protein glycosylation of SARS-CoV-2, provides the virus with an effective camouflage against host immune system recognition.[1] A blood type O individual can thus infect a blood type A individual, with the resultant virus replication producing blood type A SARS-CoV-2. Blood type association with SARS-Cov-2 infection is underlined by virus hijacking host cell machinery enzymes involved in blood type glycosylation by glycotransferases indicating inhibition of these enzymes as a possible treatment for covid-19.

The evaluation of miglustat Covid-19 treatment effectiveness was previously investigated In Vitro revealing no impact in the diseaes.[8] In a paper by Nunes-Santos et al, miglustat treatment had no impact on receptor binding of SARS-CoV-2 spike protein to the ACE2 receptor.[8] In addition, although cytokine production was enhanced in both the miglustat treated spike protein and non-treated spike protein stimulation of peripheral blood mononuclear cells (PBMCs) there was no difference in cytokine production between them.[8] Understanding the relationship between blood type and SARS-Cov-2 infection susceptibility and replication without immune system recognition reveals a mechanism explaining asymptomatic and presymptomatic patients with coronavirus. In these patients no immune response has been initiated suggesting a lack of cytokine production. A study by Long et al., confirms asymptomatic Covid-19 patients have no difference in cytokine production when compared to healthy individuals.[9] The In Vitro model of spike protein stimulation of PBMCs by Nunes-Santos et al does not reflect In Vivo coronavirus infection, since In Vivo SARS-CoV-2 spike protein glycosylation prevents immune system recognition.[1] Therefore, experiments revealing no difference in cytokine production with and without miglustat treatment are comparing two antigenic

proteins. A proposed mechanism of action for miglustat in Covid-19 treatment is the inhibition of spike protein glycosylation resulting in SARS-CoV-2 recognition by the immune system. Evaluation of miglustat treatment for Covid-19 patients should illicit production of cytokines resulting in fever which will work as an early marker of treatment effectiveness. Finally, Covid-19 infected patients with Gaucher disease were initially suspected to be highly vulnerable to viral infection, however, reports have shown no hospitalization amongst this group. [10, 11] Whether glycotransferase inhibitors are playing a role in decrease hospitalization of gaucher disease patients has yet to be determined.[10,11] Miglustat is a FDA approved medication for treatment of Gaucher disease at 100mg three times a day and Niemann-Pick Type C disease at 200mg three times day.[12]

The implication of extensive SARS-CoV-2 glycosylation is seen in the increased severity of Covid-19 in diabetic patients with high hemoglobin A1C.[13] A study by Merzon et al showed pre-infected patients with a hemoglobin A1C of greater than 9% was a risk factor for Covid-19 severity.[13] As with diabetic individuals where high hemoglobin A1C results in more extensive glycosylation of red blood cells, SARS-CoV-2 spike protein may be further glycosylated in this environment. Increased SARS-CoV-2 spike protein glycosylation would lead to an improved virus glycan shield, providing an effective barrier against immune system recognition.

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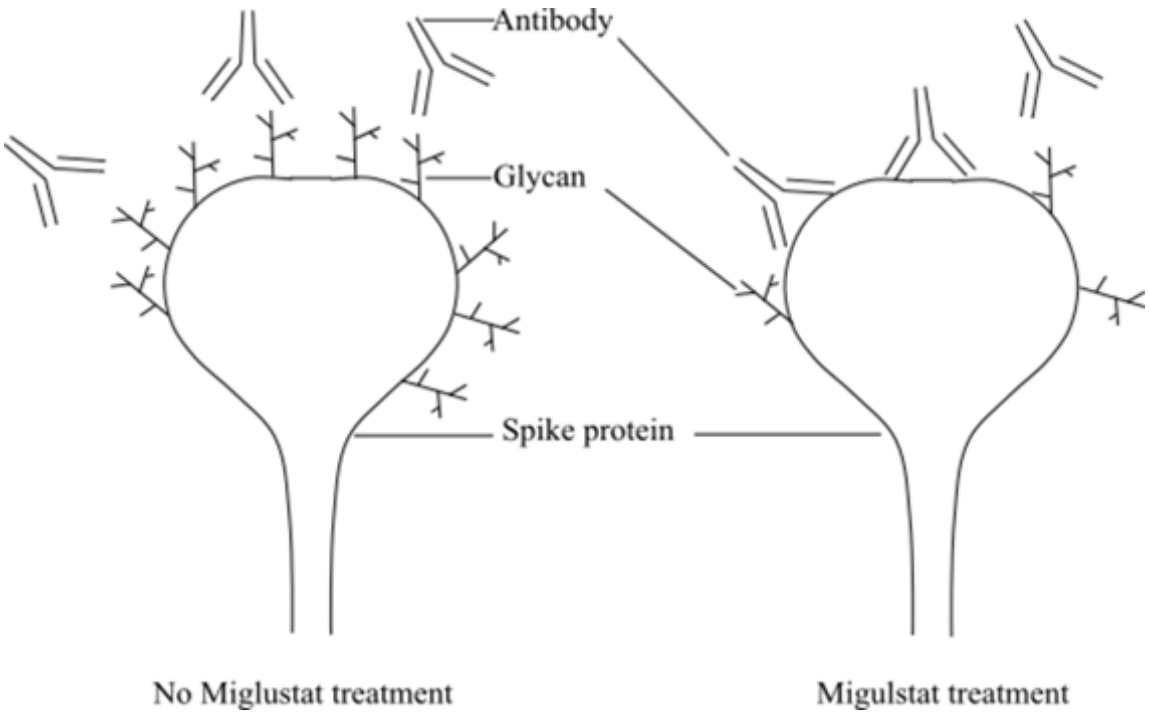

Figure 1. Miglustat treatment of SARS-CoV-2 spike protein and immune system recognition.

Results

Recipient Blood Types	Donor Blood Types: O	B	A	AB	TOTAL
AB	46%	9%	42%	3%	100%
A	46%		42%		88%
B	46%	9%			55%
O	46%				46%

Blood type percentage is representative of the Canadian population.

Table 1. Susceptibility to SAR-Cov-2 based on recipient blood types and their percentage represented in the population.

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