Miglustat: A glycotransferase inhibitor for Covid-19 treatment

Dean Tatlow[1]

1 Alberta Health Services

Funding: The author(s) received no specific funding for this work.

Potential competing interests: The author(s) declared that no potential competing interests exist.

Abstract

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

Miglustat: A glycotransferase inhibitor for Covid-19 treatment.

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 that it is unlikely to impact the course of the disease.[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, in addition there was no effect on cytokine production in stimulation of PBMC.[8] Understanding the relationship between blood type and SARS-Cov-2 infection susceptibility and replication without immune system recognition reveals a mechanism for treatment. Alternatively, our proposed mechanism of action for miglustat is the prevention of glycan coat formation on the SARS-CoV-2 spike protein allowing for immune system recognition. In vivo SARS-CoV-2 spike protein glycosylation prevents immune system recognition.[1] The

In Vitro models by Nunes-Santos et al do not reflect that seen In Vivo, since HEK293T cells used to produce the spike protein glycosylation are immunologically different from the peripheral blood mononuclear cells (PBMCs). Therefore, experiments revealing no difference in cytokine production with and without miglustat treatment are comparing two antigenic proteins. However, there is evidence from Ninues-Santos et al showing the SARS-Cov-2 protein is modified by miglustat and this modification produces an immune response.[8] Thus, it is possible for miglustat to be an effective treatment for Covid-19 by allowing for immune system recognition of the SARS-Cov-2 spike protein. Miglustat antiviral mechanism of actions lies in the glycotransferase inhibition of SARS-CoV-2 spike protein glycosylation, which exposes the spike protein to immune recognition. The FDA approved dosage of miglustat for treatment of Gaucher disease is 100mg three times a day and Niemann-Pick Type C disease is 200mg three times day.[9]

The implication of extensive SARS-CoV-2 glycosylation is seen in the increased severity of Covid-19 in diabetic patients with high hemoglobin A1C.[10] 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.[10] 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.

Understanding the glycosylation of SARS-CoV-2 by host cells has important implications in vaccine development by allowing for prediction of vaccine effectiveness. In this model SARS-CoV-2 vaccines based on mRNA and DNA will by modified by the host cells and obtain a glycan coat similar to the host. This will result in the specific production of antibodies towards areas of the spike protein that are not covered by the glycan coat. Conversely, vaccines produced by inactivated virus or subunit vaccines will not obtain the host type glycan shield resulting in a more diverse production of antibodies. Thus, the neutralizing antibodies are more likely to be developed by mRNA and DNA vaccines. Early results are suggestive of this process with Moderna, Pfizer-BioNTech, and Oxford vaccine over 90% protection, whereas CoronaVac an inactivated virus vaccine obtains 50.4% protection.[11,12,13,14]

ACKNOWLEDGEMENTS

Thank-you Stanley Vindevoghel

REFERENCES

1.Grant, O.C., Montgomery, D., Ito, K. et al. Analysis of the SARS-CoV-2 spike protein glycan shield reveals implications for immune recognition. Sci Rep 2020;**10,** 14991

2.Guillon P, Clément M, Sébille V, et al.Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies.Glycobiology. 2008;18(12):1085-1093.

3. Canadian blood services. Understanding your blood type. 2020. https://www.blood.ca/en/blood/donating-blood/whats-

my-blood-type

4. Hoiland, R. L., Fergusson, N. A., Mitra, A. R., Griesdale, D. E. G., Devine, D. V., Stukas, S., Cooper, J., Thiara, S., Foster, D., Chen, L. Y. C., Lee, A. Y. Y., Conway, E. M., Wellington, C. L., and Sekhon, M. S. The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19. 2020;Blood Adv. 4, 4981– 4989.

5.Ellinghaus D, Degenhardt F, Bujanda L, et al; Severe Covid-19 GWAS Group. Genomewide association study of severe Covid-19 with respiratory failure.N Engl J Med. 2020.

6.M. B. Barnkob, A. Pottegård, H. Støvring, et al; Reduced prevalence of SARS-CoV-2 infection in ABO blood group O, Blood Advances 2020;4,4990–4993 .

7.Ahmad Abu Turab Naqvi, Kisa Fatima, Taj Mohammad, Urooj Fatima, Indrakant K. Singh, Archana Singh, Shaikh Muhammad Atif, Gururao Hariprasad, Gulam Mustafa Hasan, Md. Imtaiyaz Hassan,
Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach, Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2020 Volume 1866, Issue 10.

8. Nunes-Santos CJ, Kuehn HS, Rosenzweig SD. N-Glycan Modification in Covid-19 Pathophysiology: In vitro Structural Changes with Limited Functional Effects. J Clin Immunol. 2020 Nov 27:1–10.

9. Miglustat(Systemic). In: Lexi-Drugs. Lexi-Comp, Inc. Updated November 24, 2020. Accessed December 20, 2020.

10.Merzon E, Green I, Shpigelman M, et al. Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes. Diabetes Metab Res Rev 2020.

11.Mahase, E. Covid-19: Moderna vaccine is nearly 95% effective, trial involving high risk 623and elderly people shows. BMJ: British Medical Journal (Online)371, 2020.

12.Mahase E. Covid-19: Pfizer vaccine efficacy was 52% after first dose and 95%after second dose, paper shows. BMJ. 371,2020.

13.Mahase, E. COVID-19: Oxford vaccine is up to 90% effective, interim analysis indicates. BMJ 371,2020 m4564.

14.https://www.bbc.com/news/world-latin-america-55642648

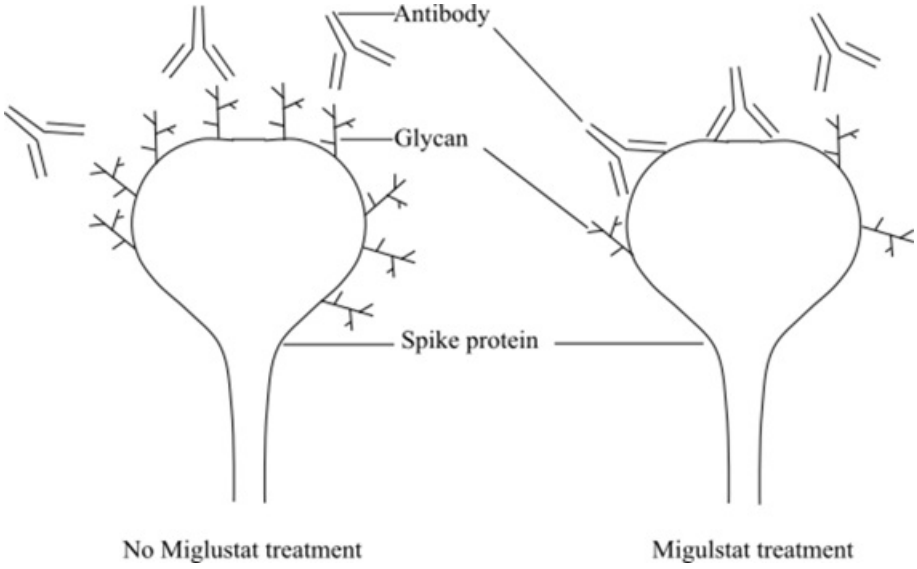

Figure 1. Miglustat treatment of SARS-CoV-2 spike protein and immune system recognition.

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%

RESULTS

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

Blood type percentage is representative of the Canadian population.