Increased COVID-19 Mortality in geographies with higher prevalence of the Pi*SZ Alpha 1 Antitrypsin Genotype

Mihael H. Polymeropoulos, MD
Vanda Pharmaceuticals Inc.
2200 Pennsylvania Ave NW, Suite 300-E, Washington, D.C. 20037
mihael.polymeropoulos@vandapharma.com

Abstract

As of the time of this paper, more than 800,000 people have been confirmed to be infected by the COVID-19 virus and over 40,000 people have died. In this paper we have identified a correlation between the geographic prevalence of the Pi*SZ genotype of the alpha 1 antitrypsin gene (A1AT) and COVID-19 mortality. This observation if confirmed and extended, would suggest that patients carrying the Pi*SZ A1AT genotype may be at increased mortality risk due to COVID-19 infection. Additionally, this observation may offer new therapeutic opportunities for COVID-19 induced respiratory distress through the development and use of elastase inhibitors or A1AT enhancers.

SARC-CoV2 and COVID-19 infection

COVID-19 is caused by the novel SARS-CoV2 virus that originated in China in December of 2019. As of the time of this paper, more than 500,000 people have been confirmed to be infected by the COVID-19 virus and over 25,000 people have died. The pandemic is in progress with exponential growth of new cases across the globe and most recently the United States. Efforts are underway for development of therapeutics including vaccines and antiviral agents. It is very important, however, not to ignore that efforts should also focus towards helping patients that experience Acute Respiratory Distress Syndrome (ARDS). It appears that some patients progress rapidly and abruptly to respiratory failure requiring mechanical ventilation. One of the markers of decompensation is the increase of D-Dimers in the blood [1].

Human Leukocyte elastase, D-Dimers and alpha 1 antitrypsin

D-Dimers are a breakdown product of a blood clot once the clot is broken down by fibrinolysis, also referred to as fibrin degradation products (FDP). D-Dimers are seen in inflammatory conditions and are believed to be a reflection of the activity of plasmin and elastase, two key proteases. The human leukocyte elastase (HLE) participates in fibrinolysis and its activity produces D-Dimers and also cleaves a number of other proteins, including elastin. Leukocyte elastase is derived from granulocytes which are often elevated during inflammation and are part of the host immune response. Increased activity of elastase in the lung is associated with emphysema [2]. A prevailing hypothesis in the pathogenesis of Chronic Obstructive Pulmonary Disease (COPD) is the disturbance of the balance of proteases and their inhibitors, and specifically HLE and its natural inhibitor alpha 1 antitrypsin (A1AT). Moreover, extensive

genetic evidence has shown that individuals with hereditary alpha 1 antitrypsin deficiency develop emphysema in adulthood.

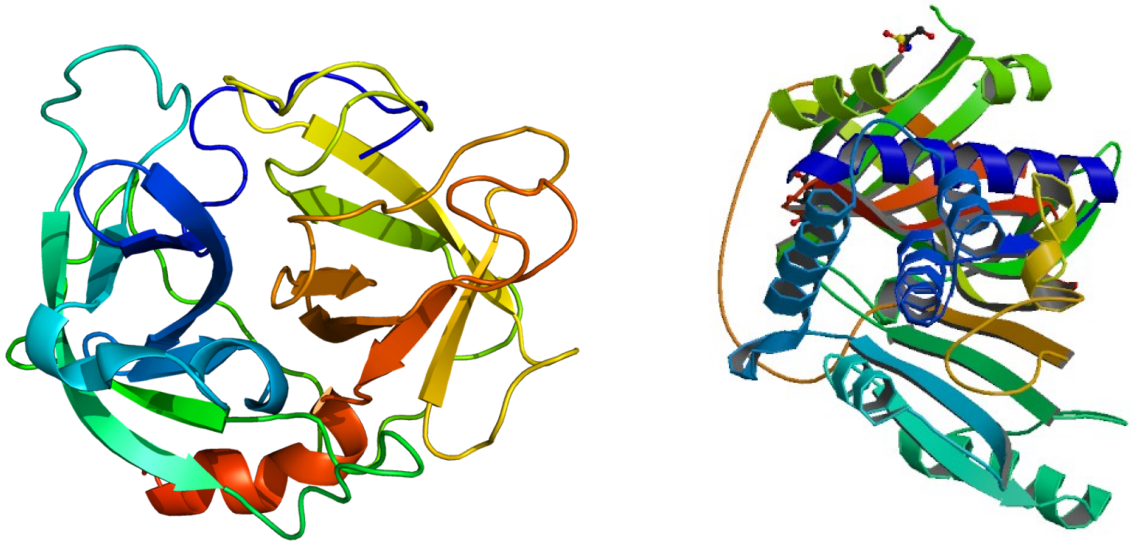
COVID-19 ARDS and increased Human Leukocyte Elastase activity

The pathophysiology of ARDS in COVID-19 has not been elucidated yet. We hypothesize that the viral infection leads to an inflammatory host response, especially in the lung, which leads to sequestration and activation of granulocytes in the lower respiratory tract and the alveoli. Significant evidence exists that HLE is responsible for the depletion of at least one of the surfactant proteins, surfactant protein D (SP-D) during inflammation of the lung. Surfactant proteins A, B, C and D are part of the surfactant which is produced by type II alveolar cells and functions to lower surface tension in the interphase between the liquid and air phases at the alveoli. We hypothesize that an increase in the activity of HLE at the alveoli can lead to the rapid and catastrophic deterioration of respiratory function in patients with ARDS secondary to COVID-19 infection. If true, this theory presents a number of potential therapeutic opportunities including some immediate ones.

Figure 1:

a) 3D structure of the Human Neutrophil Elastase protein [3]
b) 3D structure of alpha 1 antitrypsin [4]

a) b)



Alpha 1 Antitrypsin Deficiency (AAT) allele carriers and risk for COVID-19 ARDS

Individuals who are carriers of genetic polymorphisms that lead to AAT would be predicted to be at increased risk of ARDS associated with COVID-19 infection. Given that the rapid pandemic has overwhelmed health care systems, it is important to identify individuals with the highest risk of mortality. It has been discussed that older individuals and individuals with underlying medical conditions are at higher risk for severe complications and death. However, differences in outcomes exist in this population and additionally with the expansion of the infected population it is now apparent that younger people without any apparent underlying conditions are becoming severely ill and some of them are dying of acute respiratory failure. It is imperative that we conduct the necessary epidemiological analysis rapidly, and share the data broadly, in order to better assess and identify individuals at risk who may require additional and urgent interventions.

Europe has recently been the epicenter of the COVID-19 epidemic which is associated with a high prevalence of ARDS and associated mortality. We have reviewed the prevalence of AAT alleles reported in the literature as well as the emerging COVID-19 mortality data and there appears to be a trend of higher mortality in populations that are have higher allele frequency for either the S or the Z AAT alleles. In the review by Blanco et al [5], they reported the following: "In Europe, the mean SZ prevalence by regions (from the highest to the lowest) was as follows: Southern Europe, 1 SZ per 483 subjects (1:483); Western Europe, 1:581; Northern Europe, 1:1,492; Central Europe, 1:1,712; and Eastern Europe, 1:11,818" [5].

In our hypothesis, higher COVID-19 mortality would be expected in Southern Europe and lower mortality in central and Eastern Europe.

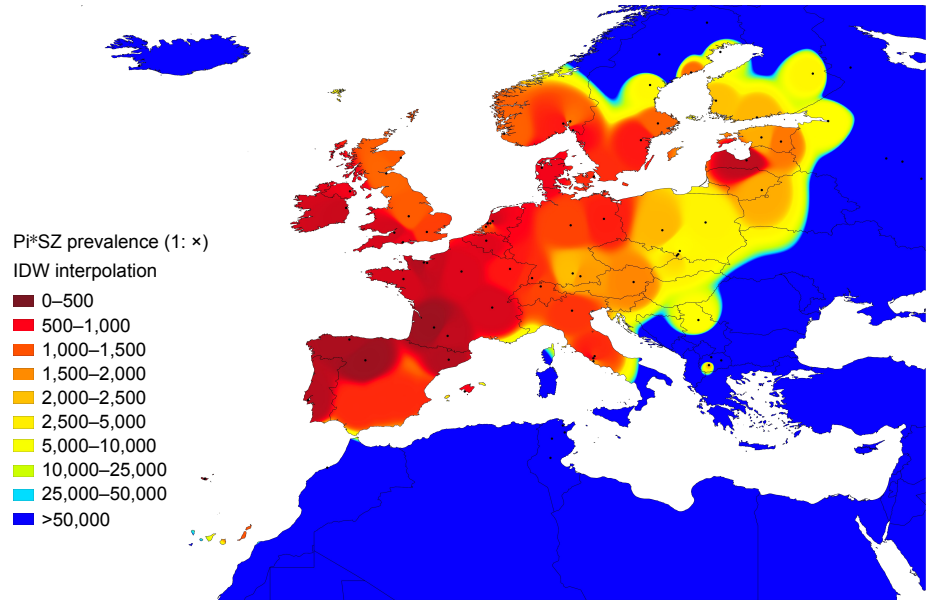


Figure 1
This figure is from Blanco et al [5]. showing a heat map of Pi*SZ prevalence in Europe

As it can be seen in this Figure from Blanco et al [5], the prevalence of the PI*SZ genotype is more prevalent in Southern Europe and less prevalent in Central Europe. It should also be noted that the Italian peninsula shows higher prevalence in the North as compared to the South where the prevalence is very low.

We have analyzed the accumulating data for mortality during to COVID-19 infections (March 31, 2020) and performed a correlation analysis between mortality rate (defined as deaths/cases confirmed) and the reported prevalence of the Pi*SZ A1AT gene allele by country. For robustness we have included only for the 9 EU countries that have so far reported over 10,000 confirmed cases. Results of this correlation analysis are shown in Table 1. A significant correlation of R=0.66 (pvalue=0.05) was observed using all 9 country mortality rate and Pi*SZ prevalence. From Blanco et al (2017), we observe that there is a significant difference in prevalence of the Pi*SZ genotype between North Italy (higher) and South Italy (lower). We have therefore reanalyzed the data this time excluding Italy. In this analysis also shown in Table 1, (excluding Italy), the correlation between mortality rate and Pi*SZ prevalence is even stronger R=0.88 (pvalue=0.003) Table 1.

These results are suggestive that a Pi*SZ genotype status may be a risk factor for COVID-19 ARDS and resulting mortality. With further confirmation this observation may suggest that a different therapeutic approach is instituted for patients with COVID-19 infection and the Pi*SZ genotype that can include aggressive supportive therapy and the institution of elastase activity reducing treatments that may include small molecule inhibitors of the enzyme and/or supplementation of the A1AT activity.

Table 1: Correlation between geographic COVID-19 mortality and Pi*SZ genotype

Country	Cases	Deaths	Deaths/Cases	Pi*SZ (1 in x)
Italy	105792	12428	0.117475802	967
Spain	94417	8269	0.087579567	278
France	44550	3024	0.067878788	413
Germany	68180	682	0.010002933	1337
Switzerland	16186	395	0.024403806	1152
Belgium	12775	705	0.05518591	551
Austria	10109	128	0.012661984	1680
Netherlands	12595	1039	0.082493053	617
UK	25150	1789	0.071133201	900
Pearson's Correlation				
All Countries (n=9)		R=0.66	pvalue =0.05	
Excluding Italy (n=8)		R=0.88	pvalue=0.003	

Human Leukocyte Elastase (HLE) inhibitors in the treatment of COVID-19 ARDS

There has been interest in the development of HLE inhibitors for the treatment of emphysema and the treatment of patients with inherited forms of alpha 1 antitrypsin (A1AT) deficiency.

Sivelestat

Sivelestat is currently available in Japan and Korea for the treatment of Acute Lung Injury (ALI) including ARDS. A number of clinical studies [6] support the therapeutic utility of sivelestat in ARDS [6]. Nonetheless the magnitude of the clinical benefit is still debated. In one Phase III study in 230 ventilated patients with ALI, sivelestat reduced duration of mechanical ventilation and shortened ICU stay, however, no significant effect was seen on the 30 day survival rate. In another study of 492 patients there was no effect on the ventilator free days or 28 day all cause mortality. However, in a postmarketing study designed to reevaluate the efficacy of sivelestat in 404 ALI patients and 177 controls, sivelestat significantly improved the number of ventilator free days. While the differences in the results of these studies may have been due to differences in the study population and the design of the study, sivelestat is currently widely used in Japan and Korea in the ICU setting for patients with ARDS.

Zemaira®

Zemaira® is an alpha-proteinase inhibitor (A1-Pi) approved by the U.S. Food and Drug Administration and is indicated for chronic augmentation and maintenance therapy in adults with A1AT deficiency and clinical evidence of emphysema [7]. Zemaira® is not approved for lung disease patients for whom severe A1AT deficiency has not been established.

Alvelestat (MPH996)

Alvelestat is an experimental leukocyte elastase inhibitor under development in the US for the treatment of patients with alpha 1 antitrypsin deficiency of PI*ZZ, PI*SZ or PI*Null/Null genotype. According to NCATS “the drug's clinical profile suggests that it will be well tolerated with few, if any, side effects, and the existence of simple methods that can indirectly measure its activity in vivo” [8,9].

Conclusion

We have observed correlation of higher COVID-19 mortality in geographies with higher prevalence of the Pi*SZ genotype. If confirmed this may suggest specific therapeutic options and treatment plan for these patients. Limitations of this study that include the need for direct observations of genotype and mortality data in Pi*SZ carriers as well as the examination of potential yet unknown confounders, would need to be examined in further investigations across different geographies and populations.

References:

[1] Seitz R, Lerch L, Immel A, Egbring R. D-dimer tests detect both plasmin and neutrophil elastase derived split products. Ann Clin Biochem 1995;32:193-5. https://doi.org/10.1177/000456329503200211.

[2] Demkow U, van Overveld FJ. Role of elastases in the pathogenesis of chronic obstructive pulmonary disease: implications for treatment. Eur J Med Res 2010;15(Suppl. II):27-35. https://doi:10.1186/2047-783x-15-s2-27.

[3] RCSB Protein Data Bank, 5A8Y, crystal structure of human neutrophil elastase in complex with a dihydropyrimidone inhibitor, http://www.rcsb.org/structure/5A8Y; 2016 [accessed 30 March 2020].

[4] RCSB Protein Data Bank, 1ATU, structure of uncleaved alpha-1-antitrypsin, http://www.rcsb.org/structure/1ATU; 1997 [accessed 30 March 2020].

[5] Blanco I, Bueno P, Diego I, Perez-Holanda S, Lara B, Casas-Maldonado F, et al. Alpha-1 antitrypsin Pi*SZ genotype: estimated prevalence and number of SZ subjects worldwide. Alpha-1 antitrypsin Pi*SZ genotype: estimated prevalence and number of SZ subjects worldwide. Int J Chron Obstruct Pulmon Dis 2017;12:1683-94. https://doi.org/10.2147/COPD.S137852.

[6] Aikawa N, Kawasaki Y. Clinical utility of the neutrophil elastase inhibitor sivelestat for the treatment of acute respiratory distress syndrome. Ther Clin Risk Manag 2014;10:321-9. https://doi.org/10.2147/TCRM.S65066.

[7] Zemaira, Zemaira alpha-1-proteinase inhibitor, https://www.zemaira.com/; 2020 [accessed 30 March 2020].

[8] National Center for Advancing Translational Sciences, Inxight: Drugs, ALVELESTAT 6Y5629322X, https://drugs.ncats.io/drug/6Y5629322X; 2020 [accessed 30 March 2020].

[9] Stevens T, Ekholm K, Gränse M, Lindahl M, Kozma V, Jungar C, et al. AZD9668: pharmacological characterization of a novel oral inhibitor of neutrophil elastase. J Pharmacol Exp Ther 2011;339(1):313-20. https://doi.org/10.1124/jpet.111.182139.