



LETTER TO THE EDITOR

Potential resistance to SARS-CoV-2 infection in lysosomal storage disorders

Maurizio Pieroni¹, Federico Pieruzzi^{2,3}, Renzo Mignani⁴, Francesca Graziani⁵, Iacopo Olivetto⁶, Eleonora Riccio⁷, Michele Ciabatti¹, Giuseppe Limongelli⁸, Raffaele Manna⁹, Leonardo Bolognese¹ and Antonio Pisani⁷

¹Cardiovascular Department, San Donato Hospital, Arezzo, Italy, ²Clinical Nephrology, School of Medicine, University of Milano Bicocca, Milan, Italy, ³Nephrology and Dialysis Unit, ASST-Monza San Gerardo Hospital, Monza, Italy, ⁴Department of Nephrology, Infermi Hospital, Rimini, Italy, ⁵Cardiovascular Department, Policlinico Gemelli, Catholic University, Rome, Italy, ⁶Cardiomyopathy Unit, Careggi Hospital, Florence, University Florence, Italy, ⁷Department of Public Health, Nephrology Unit, University of Naples 'Federico II', Naples, Italy, ⁸Department of Translational Medical Sciences, University of Campania 'Luigi Vanvitelli', Naples, Italy and ⁹Department of Internal Medicine, Policlinico Gemelli, Catholic University, Rome, Italy

Correspondence to: Maurizio Pieroni; E-mail: mauriziopieroni@yahoo.com

On 11 March 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak to be a 'pandemic'. In the following months, the disease spread in Italy to include >2 million infected patients (3.7% of the population), with >80 000 COVID-19-related deaths. While vaccines have been developed, based on the current knowledge of biology of coronavirus infection, COVID-19 is empirically treated with antivirals, immunomodulatory and antimalarial drugs, but most of these approaches do not specifically target the cellular mechanisms involved in viral entry and spreading.

It has been demonstrated that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects human and some animal cell lines through the Angiotensin-converting enzyme 2 (ACE2) receptor, but the endocytic pathway represents an alternative entry route for SARS-CoV-2 and other several viruses, including Ebola virus and African swine fever virus. The endosomal protein, Niemann–Pick C1, deficiency in which causes the lysosomal disorder Niemann–Pick disease type C (NPC), has been identified as a necessary entry receptor for Ebola virus [1, 2]. Similarly, it is well established that SARS-CoV-2 infection requires an acidic endosomal environment [3]. Of note, endosome luminal pH and further vesicle maturation are controlled by ion channels, pumps and membrane proteins, suggesting

that drugs targeting these structures may potentially have broad-spectrum antiviral properties. Indeed, recent studies have described the inhibitory effect of experimental and Food and Drug Administration-approved drugs acting on the endosomal compartment against viruses of high relevance for human and animal health, including SARS-CoV-2 and Ebola virus (Figure 1A) [4].

In Fabry disease, the genetically determined deficit of alpha-galactosidase A leads to glycosphingolipids accumulation in kidney, heart, vessels and lungs. Glycosphingolipid storage causes impairment of several lysosomal functions including endosomal maturation and autophagy processes (Figure 1B) [5], thus leading to an 'unfavourable' host cellular environment that may interfere with infection and propagation of some viruses. We therefore hypothesized that patients with Fabry disease may be less prone to SARS-CoV-2 infection and COVID-19 severe clinical manifestations.

We assessed the clinical prevalence of COVID-19 between 1 February and 30 April 2020, in a population of 234 patients with established Fabry disease from six referral centres in Italy. Among 234 patients, only 1 (0.4%) was affected by mild COVID-19 not requiring hospitalization. No patient died. Four patients with affected relatives were reported as asymptomatic carriers

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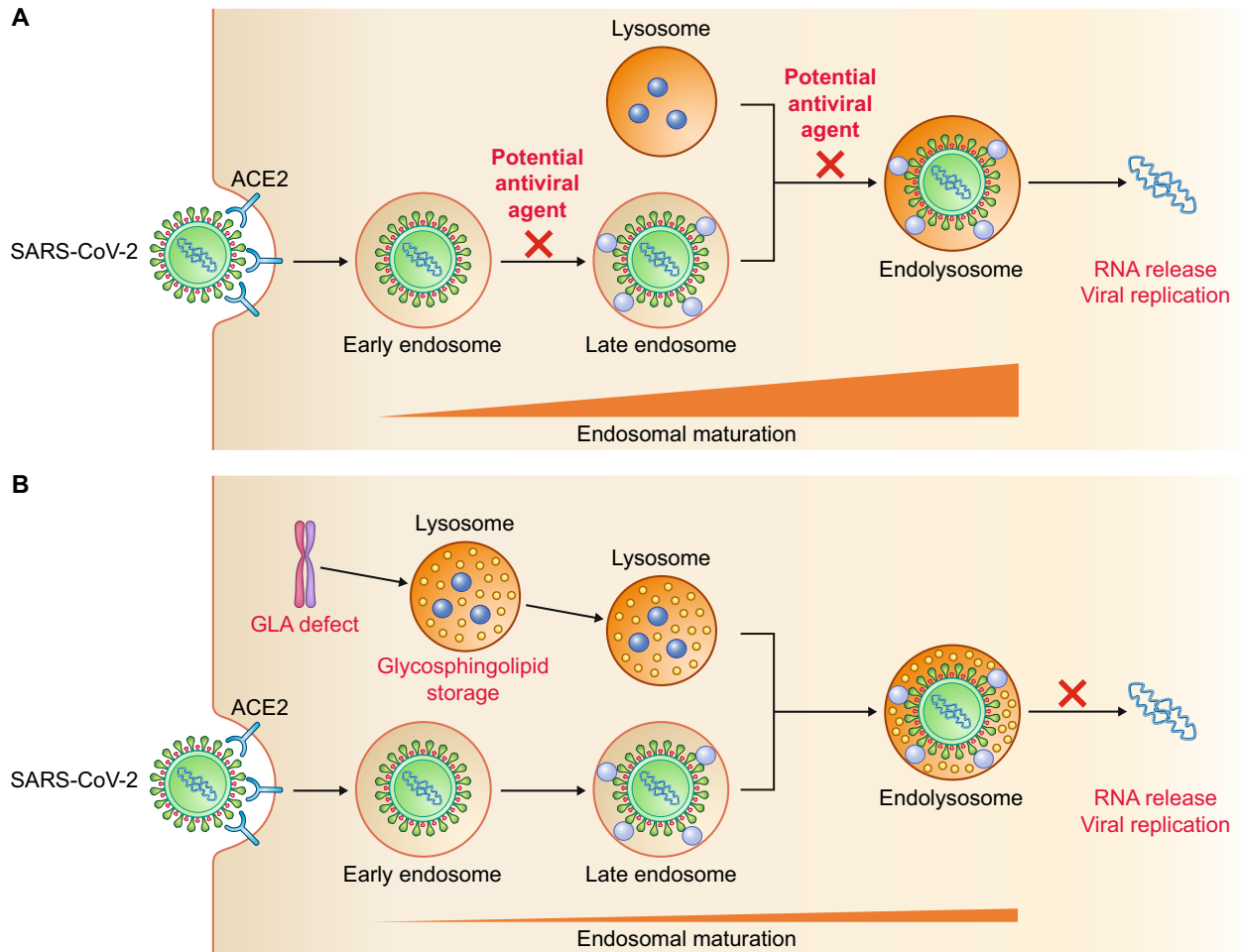


FIGURE 1: Proposed mechanism of potential resistance to SARS-CoV-2 infection in lysosomal storage disorders. (A) Role of the endocytic pathway and lysosomes in SARS-CoV-2 cellular infection and spreading in normal conditions with normal endosomal maturation. Possible site of action of experimental or repurposed drugs is indicated. (B) Impairment of endosomal maturation and endocytic pathway in lysosomal storage disorders, determining a potential resistance to SARS-CoV-2 infection and spreading.

Table 1. Clinical features of patient population

Variable	Overall, n = 234	Males, n = 107 (46%)	Females, n = 127 (54%)
Age, years, mean ± SD	46.3 ± 17.6	45.6 ± 17.9	47.0 ± 17.8
Age >60 years, n (%)	57 (24)	26 (18)	31 (24)
Age <18 years, n (%)	11 (5)	8 (7)	3 (2)
Residents in Lombardia, n (%)	50 (21)	18 (17)	32 (25)
Residents in Emilia-Romagna, %	59 (25)	30 (28)	29 (23)
Diabetes, %	10 (4)	8 (7)	2 (2)
Hypertension, %	46 (20)	29 (27)	17 (13)
Classic Fabry disease, %	147 (63)	65 (61)	82 (65)
Late-onset Fabry disease, %	87 (37)	42 (39)	45 (35)
Chronic kidney disease, %	35 (15)	25 (23)	10 (8)
Dialysis, %	15 (6)	9 (8)	6 (0.5)
Kidney transplant, %	11 (5)	11 (10)	0
ERT, %	139 (59)	72 (67)	67 (52)
Home ERT (% of ERT patients)	85 (61)	39 (36)	46 (36)
Patients with ERT interruption	23 (10)	13 (12)	10 (8)
Missed ERT infusions, n (% of scheduled)	26 (1.6)	16 (1.5)	10 (1.2)
Chaperone therapy, %	24 (10)	13 (12)	11 (9)
Other therapies in clinical trials	4 (2)	4 (4)	0
COVID-19+ with symptoms, %	1 (0.4)	0	1 (0.8)
COVID-19+ without symptoms, %	2 (0.8)	0	2 (1.6)
SARS-CoV-2 antibody+ with negative nasal swab	2 (0.8)	1 (0.1)	1 (0.8)

(two patients) or positive for SARS-CoV-2 immunoglobulin G with negative swab (Table 1). Interestingly, all but one of the infected Fabry patients was females. As Fabry disease is an X-linked disorder, females usually present a mild-to-moderate residual enzymatic activity leading to a partially preserved lysosomal function. Among 143 patients receiving enzyme replacement therapy (ERT), most (90%) continued treatment either in hospital (63%) or at home (37%), missing only 1.6% of scheduled therapy infusions, although some cases were at higher risk of severe COVID-19 complications due to comorbidities or previous kidney transplant (Table 1). Of note, 35% of the patient population was represented by patients resident in Italian regions of Lombardia (21%) and Emilia-Romagna (25%), which were most affected by the COVID-19 pandemic during the first pandemic wave.

Given the prevalence of COVID-19 in Italy, even considering the potential bias of a possible voluntary self-quarantine adopted by Fabry patients to avoid the contagion, these observations, together with the biological premises, support the hypothesis that an impaired lysosomal function may protect patients with lysosomal storage disorders from SARS-CoV-2 infection and from severe clinical manifestations, although affected by a systemic multi-organ disease [6]. A similar hypothesis has been proposed for other lysosomal disorders, including NPC [2, 3].

Our findings, together with mechanistic premises, although they do not provide robust scientific evidence of a potential resistance to COVID-19 in Fabry disease, are hypothesis-generating and suggest that further studies including *in vitro* experiments and a more extensive epidemiological evaluation

with widespread serological assessment of Fabry patients could confirm this hypothesis and provide new avenues for therapeutic strategies against SARS-CoV-2 infection.

CONFLICT OF INTEREST STATEMENT

None declared.

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