WHAT IS KNOWN AND OBJECTIVE

The SARS-CoV-2 outbreak poses major therapeutic problems, and there is an urgent need for a specific antiviral agent to treat this infection, thus decreasing viral shedding and subsequent transmission. Although numerous clinical trials are in progress and patients at different disease severity stages have been targeted, the vast majority of these trials are for treatment purposes and not preventive purposes (1,628 trials versus 289 trials, cf Living mapping and living systematic review of COVID-19 studies at https://covid-nma.com/dataviz; 28 October 2020). Initial trials in the search for an effective therapeutic yielded disappointing results (1,2) and the strategy of repurposing marketed drugs offers new opportunities. (3) The so-called “drug repurposing” strategy actually includes several different methodological approaches, and to date, the most successful examples of drug repurposing have not involved a systematic approach but rather serendipity.(3) In the repositioning strategy the first step, that is the identification of the candidate molecule(s) for a given indication is critical. The approaches that address this step are either experimental and/or computational.(3) Among the potential approaches, exciting new opportunities are afforded by the use of new data sources—including clinical data repositories.

Numerous organic molecules, including currently marketed drugs, have the potential to functionally inhibit, in a reversible and additive manner, the activity of acid sphingomyelinase (ASM) which is a lysosomal glycoprotein involved in a wide range of disorders (4) including virus infections. These molecules identified by the
acronym FIASMA (ie functional inhibitors of acid sphingomyelinase) have the potential to disrupt the entry of viruses into cells. The purpose of this study was to provide a rationale for repurposing of FIASMAs (functional inhibitors of ASM) for the prophylactic and/or therapeutic treatment of SARS-CoV-2 infections through a literature search in PubMed and the medRxiv.org preprint server for Health Sciences.

2 | COMMENT

2.1 | FIASMA’s (see Supplement material for a list of FIASMAs)

Acid sphingomyelinase (ASM) is a lysosomal glycoprotein anchored to the inner lysosomal membrane. Under specific stimuli, ASM is translocated to the external leaflet of the cell membrane under specific stimuli where it catalyzes the hydrolysis of sphingomyelin into ceramide and phosphorylcholine. Sphingomyelin is the most abundant sphingolipid component of the mammalian plasma membrane where it is associated with cholesterol in lipid rafts. ASM inhibitors work either by direct inhibition or by functional inhibition (FIASMA). Functional inhibitors of ASM (FIASMAs) are cationic amphiphilic molecules; they are relatively heterogeneous in terms of chemical structure but have several shared characteristics. In general, FIASMAs are polycyclic molecules, with at least one basic nitrogen atom (pKa > 4) which corresponds to a partially protonated functional group at acidic pH, showing moderate to high lipophilicity (log p > 3).

The internal wall of lysosomes is negatively charged due to the abundant presence of phospholipids. Several positively charged proteins form electrostatic interactions with the internal wall of the lysosome, and this protects them from lysosomal degradation. ASM is attached to the lysosomal membrane through this mechanism. FIASMAs are integrated into the lysosomal membrane through their lipophilic components, presenting their positively charged component to the lysosomal lumen. FIASMA activity results in the detachment of the ASM from the lysosomal membrane and its subsequent proteolytic degradation in the lysosomal lumen. Hence, ASM-activating stimuli cannot effect the translocation of ASM to the external leaflet of the cell membrane, resulting in the perturbation of the activities downstream of this signalling cascade, including lipid raft formation (Figure 1).

However, residual ASM activity is necessary for cell viability. There are significant differences in the intra-lysosomal capture speed depending on lipophilicity (logP) and degree of ionization (pKa) from minutes to hours in cell culture systems. Indeed, desipramine, fluoxetine, maprotiline, paroxetine and protriptyline have rapid lysosomal capture (<30 min) with moderate lysosomal accumulation (lysosome/extracellular concentration ratio <100:1).(6) Drugs with significant FIASMA activities (residual activity <50% at a concentration of 10 µM) have been previously characterized (6-8) and are listed in a table as Supplementary material.

2.2 | FIASMA’s and coronaviruses

In general, viruses exploit the cellular mechanisms of endocytosis to penetrate the cytosol. However, several different mechanisms of internalization may be involved, including clathrin-mediated endocytosis, macropinocytosis, caveolar/lipid raft-mediated endocytosis, or one of several incompletely characterized clathrin-independent and caveolin/lipid raft-independent mechanisms.(9) During infection with Coronoviridae, lipid raft-mediated endocytosis (10) and the clathrin-mediated pathway (11) have both been demonstrated to play a role in internalization, resulting in the identification of these processes as potential targets for drugs acting at the internalization step (ie fusion and entry). However, the targeting of the late compartments of the endocytic pathway after the delivery of the SARS-CoV genome to the cytoplasm is also a viable approach for the disruption of replication, as shown with the FIASMA amiodarone.(12) Indeed, various approaches targeting SARS-CoV-2 should be considered, with those targeting the virus directly likely to be the most effective.(13) However, the approaches targeting the biology of the host cells have the advantage that they are less influenced by genetic variations (which are less frequent in host cells than in viruses). As they are lysosomotropic drugs with specific activities, attention should be focused on FIASMA interference with lipid raft-mediated endocytosis following ASM inhibition (and in some cases, FIASMA interference with other steps in the endocytic pathways).

Three broad categories of experiments have been used to explore the efficacy of FIASMAs in coronavirus diseases: in silico studies (bacterial sequencing techniques, molecular modelling, whole cell simulations, etc.); and in vitro studies and in vivo studies (animal studies and clinical trials retrospective or prospective). In almost all studies, the status of the FIASMAs was not known by the authors. In the first set of studies,(11,12,14-18) the antiviral activity of FIASMAs against the SARS-CoV and MERS-CoV viruses was explored. In the second set of studies, different drugs were tested against the SARS-CoV-2 using in silico (19-29) and in vitro studies.(30-40) These are listed in Table 1. In vivo studies have been performed using either human cells infected with SARS-CoV-2 or as part of clinical studies. In a recent study using human cells, amitriptyline, desipramine, escitalopram, fluoxetine, imipramine, maprotiline, and sertraline demonstrated almost complete ex vivo inhibition of the infection of human epithelial cells (and other different human cell lines) by SARS-CoV-2 and pp-VSV-SARS-CoV-2 spike particles.(41)

Several retrospective studies in humans have suggested a better prognosis for COVID-19 patients receiving either psychotropic drugs (chlorpromazine or fluoxetine) or amlodipine. In addition, a lower prevalence of COVID-19 infections in psychiatric patients (4%) than in healthcare professionals (14%) has been reported. From these observations, suggestions of the prophylactic effect of psychoactive compounds against Sars-CoV-2 have emerged,(42-44) and a clinical trial (ie The ReCoVery study) is ongoing. Although the antiviral activity of chlorpromazine involves the inhibition of clathrin-mediated endocytosis, its FIASMA status was not mentioned.
Several other studies have identified a potential role for known FIASMAs in the treatment of COVID-19. A recently submitted study (45) explored the association between antidepressant use and the risk of intubation or death in inpatients with COVID-19. A significant association was observed between the use of any antidepressant and a reduced risk of intubation or death. When specific antidepressant use was considered, significant associations were found for escitalopram, fluoxetine and venlafaxine. Interestingly, fluoxetine is a known FIASMA. A recent retrospective study (46) on 65 inpatients who tested positive for SARS-CoV-2 and were treated or not treated with calcium channel blockers (CCB, ie nifedipine or amlodipine as FIASMA) for hypertension found that patients treated with CCB were significantly more likely to survive than those not treated with CCB (50% survival in the CCB group versus 14.6% survival in the no-CCB group). This result was confirmed in a submitted study (39) which reported that COVID-19 patients with hypertension treated with amlodipine (N = 44) for hypertension had significantly reduced mortality (3/44; 6.8%) than COVID-19 patients (N = 46) treated with other medications for hypertension (mortality: 12/46; 26%). Finally, a study (47) reporting double-blind randomized, fully remote clinical trials of fluvoxamine versus placebo found that outpatients with symptomatic COVID-19 who had been treated with fluvoxamine had a lower likelihood of clinical deterioration over 15 days than patients treated with placebo.

In total, 32 FIASMAs have been identified through in silico, in vitro or in vivo studies as potential antiviral drug candidates against SARS-CoV, MERS-CoV or SARS-CoV-2. Of these, six show activity against all three coronaviruses (chlorpromazine, clomipramine, emetine, fluphenazine, loperamide and promethazine, see Table 1). Considering the results of recent in vivo studies, four FIASMAs (amlodipine, amitriptyline and fluoxetine or fluvoxamine) merit particular interest; and their activities should be explored in future prospective studies.

It should be noted that our understanding of SARS-CoV-2 cell penetration is limited. Apart from caveolar/lipid raft-mediated endocytosis, clathrin-mediated endocytosis and micropinocytosis are potentially involved in cell entry and may themselves be modulated by FIASMAs, including chlorpromazine, sertraline and promethazine (inhibitors of clathrin-mediated endocytosis), and imipramine (an inhibitor of micropinocytosis)(48) Furthermore, the endocytic mechanisms exploited by coronaviruses may vary according to the level in the respiratory tract. Nasal epithelial cells express a wide variety of endocytic markers, whereas pneumocytes have a more restricted pattern of expression, with micropinocytosis as the predominant endocytic pathway.(48) The identification of type II alveolar pneumocytes as preferential targets of SARS-CoV-2 may explain the late alveolar damage observed in some patients.

**FIGURE 1** Mechanisms of action of functional inhibitors of acid sphingomyelinase (ASM). Left: ASM is anchored to the inner leaflet of the lysosomal membrane by electrostatic forces so that the enzyme is protected from proteolytic degradation. Specific stimuli allow the translocation of ASM from the inner lysosome to the external leaflet of the cell where ASM catalyses the hydrolysis of sphingomyelin into ceramide and phosphorylcholine. Sphingomyelin is the most abundant sphingolipid component of the mammalian plasma membrane where it is associated with cholesterol to form lipid rafts. Right: FIASMA are cationic drugs with lipophilic properties that diffuse in the lysosome by passive diffusion and potentially via an additional mechanism using ABCB1 transporter located on the lysosomal membrane. These drugs become protonated in the intra-lysosomal acidic environment and increase the intra-lysosomal pH so that ASM is detached from the inner leaflet of the lysosomal membrane and is further degraded by proteolysis. ASM translocation is no longer effective and the formation of lipid rafts is altered. Hence, different mechanisms of internalization used by viruses (ie fusion and entry) to penetrate in the cytosol of cells are altered.
### 2.3 | In vitro-to-in vivo translation

Solid evidence of antiviral activity based on in vitro and on pre-clinical studies is a prerequisite for further studies in humans. However, the in vivo translation of antiviral activity requires that the drugs have a suitable profile of drug exposure (concentration and duration) at the site(s) of action. Hence, drug pharmacokinetics and drug regimens are essential parameters for a successful translation.  

FIASMA are lipophilic, basic, amine drugs and as such have a very high volume of distribution. Indeed, amitriptyline and of chlorpromazine have steady state volume of distribution (Vdss) values of is 14.4 L per kg (49) and 8.9 L per kg. Lipophilic drugs are highly metabolized with a significant first-pass effect. The systemic clearance of amitriptyline and chlorpromazine is quite high (0.9 L/min and 1.3 L/min), and they have a low and variable oral bioavailability, ranging from 4% to 38% for chlorpromazine (50) and from 33 to 62% for amitriptyline.(49) Despite the fact that they have a high volume of distribution, the apparent elimination half-life values are not too excessively long (approx. 11 h and 18.5 h for amitriptyline and chlorpromazine), largely because of their high clearance.

| FIASMA          | SARS-CoV | MERS-CoV | SARS-CoV-2 | P-gp substrate | P-gp inhibitor |
|-----------------|----------|----------|------------|----------------|---------------|
| Amiodarone      | □        | (12,20)  |            |                |               |
| Amitriptyline   | □□□□     | (24,26,27,41) |           | +              |               |
| Amlodipine      | □□□□     | (27,28,37-39) | o          | +              |               |
| Astemizole      | □        | (16)     | □□□□       | (16,18) +      |               |
| Benztropine     | □□□□     | (16)     | □□□□       | (16) o         |               |
| Bepridil        | □□□□     | (26,35)  | +          | +              |               |
| Carvedilol      | □□□□     | (21)     | o          | +              |               |
| Cepharanthine   | □□□□     | (29,30)  | +          | +              |               |
| Chlorpromazine  | □□□□     | (11,16,17)| □□□□       | (16,18) +      | +             |
| Clemastine      | □□□□     | (19,29)  | -          | o              |               |
| Clofazimine     | □□□□     | (23,38)  | o          | +              |               |
| Clomipramine    | □□□□     | (16)     | □□□□       | (16,18) +      | +             |
| Cloperastine    | □□□□     | (16)     | □□□□       | (16,18) +      | +             |
| Desipramine     | □□□□     | (16)     | □□□□       | (16,18) +      | +             |
| Emetine         | □□□□     | (16)     | □□□□       | (16,18) +      | +             |
| Fluoxetine      | □□□□     | (22,29,31-34) | +          | +              |               |
| Fluphenazine    | □□□□     | (34)     | +          | +              |               |
| Imipramine      | □□□□     | (34)     | -          | -              |               |
| Loperamide      | □□□□     | (30)     | +          | +              |               |
| Maprotiline     | □□□□     | (41)     | -          | +              |               |
| Melatonin       | □□□□     | (21,28)  | o          | o              |               |
| Paroxetine      | □□□□     | (21)     | +          | +              |               |
| Pimozide        | □□□□     | (35)     | +          | +              |               |
| Promazine       | □□†      | (14,15)  | -          | +              |               |
| Promethazine    | □□□□     | (16)     | □□□□       | (16,18) +      | +             |
| Quinacrine      | □□□□     | (21)     | o          | o              |               |
| Sertraline      | □□□□     | (38,41)  | +          | +              |               |
| Tamoxifen       | □□□□     | (38)     | +          | +              |               |
| Trifluoperazine | □□□□     | (38)     | +          | +              |               |
| Triflupromazine | □□□□     | (38)     | +          | +              |               |
| Trimipramine    | □□□□     | (26)     | -          | +              |               |
| Thioridazine    | □□□□     | (38)     | +          | +              |               |

Note: In bold: drugs active against the 3 coronaviruses. 
in silico (□), in vitro (●), ex viv o (❖) and negative result (†). 
P-gp interaction: no information (o), positive information (+), negative information (-).
However, reaching a steady state to obtain a maximal effect would require a delay (approximately seven-times the half-life) that may prove unsuitable in an epidemic context, either for prevention or for curative use. Alternatively, a loading dose may be used to reach the steady state more rapidly, provided the tolerance profile is not a limiting factor. Furthermore, as illustrated for these two prototypic drugs, oral bioavailability is a factor of inter-individual variability that needs to be considered.

Other variability factors that may impact dosing, including renal and hepatic impairment and drug-drug interactions with concomitant medications, should also be considered especially because these drug candidates are lipophilic drugs usually with significant first-pass effect. In particular, attention should be paid to FIASMAs interacting with P-gp, either as substrate and/or as inhibitor (Table 1). P-gp is present in the lysosomal membrane (51) and P-gp substrates may have a higher lysosomal distribution than drugs only subject to passive diffusion.(52) Hence, co-administration of a strong P-gp inhibitor (eg clarithromycin, itraconazole, verapamil and some HIV protease inhibitors) with FIASMAs may decrease their lysosomal accumulation. Such features should be considered as part of a drug combination therapy in the management of SARS-CoV-2 infection.

Before prophylactic use in individual contact patients, knowledge of the pharmacokinetics in different sub-populations (including paediatrics and geriatrics) should be estimated. In addition to drug pharmacokinetics, viral kinetics must be considered to optimize dosing regimens, especially considering the limited window in which antiviral therapy can be initiated in a curative setting. Viral kinetics (ie time to peak viral load and duration of viral shedding) vary among viruses and are not yet well defined for SARS-CoV-2. These aforementioned elements are mandatory to define the initiation and of duration of any antiviral treatment.(53) Thus, precise details of drug pharmacokinetics and viral kinetics have to be known beforehand to ensure successful treatment.

2.4 | Framework of future investigations

First, retrospective investigations on confirmed COVID-19 studies should be conducted to explore the prevalence and the potential effects of FIASMAs. Indeed, it would be worthwhile to investigate whether patients infected with the SARS-CoV-2 virus who have been exposed to FIASMA’s demonstrate a more favourable evolution of the disease. Data available in the clinical hospital data warehouses may help test this assumption and to identify marketed drugs that could be repurposed. For example, in the Erasme hospital from Brussels, 370 (27%) of the 1373 cases of hospital admission for COVID-19 (March to October 2020) were prescribed at least one FIASMA. In the Rennes University Hospital, 8.5% of patients admitted for COVID-19 (55 on 642 until May 5, 2020) were treated with FIASMAs. Second, pharmaco-epidemiological studies be performed to explore whether the chronic prescription of particular FIASMAs in the general population is associated with a low prevalence of the severe symptoms of the COVID-19 infection. Third, known FIASMAs should be tested in vitro to explore their activity against SARS-CoV-2. Fourth, FIASMAs with either a protective effect in the general population or a significant activity in vitro should be tested in vivo using a notably randomized double-blinded study against a placebo.

3 | WHAT IS NEW AND CONCLUSION

The drug repurposing approach has garnered significant attention in the COVID-19 pandemic era, providing some hope of an effective treatment in the near future. Current knowledge suggests that FIASMAs should be investigated for repurposing as potential drugs against SARS-COV-2. These are small molecules showing lysosomotropism with clinically approved indications in various diseases. We strongly suggest exploring the possible protective effects of the FIASMAs in subjects treated chronically for various diseases. Furthermore, FIASMAs showing positive in those studies should be tested in off-label therapy using notably large-sized, randomized and double-blinded controlled clinical trials.

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the organizations at which the author(s) is/are employed/affiliated.

CONFLICT OF INTEREST

All the authors (PLC and GL) disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

AUTHOR CONTRIBUTIONS

All authors performed the literature search and wrote the manuscript.

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**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section.

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