Feline infectious peritonitis (FIP) and coronavirus disease 19 (COVID-19): are they similar?

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Complete List of Authors:	paltrinieri, saverio; University of Milan, Department of Veterinary Medicine; Veterinary Teaching Hospital, University of Milan Giordano, Alessia; University of Milan, Department of Veterinary Medicine; Veterinary Teaching Hospital, University of Milan Stranieri, Angelica; University of Milan, Department of Veterinary Medicine; Veterinary Teaching Hospital , University of Milan Lauzi, Stefania; University of Milan, Department of Veterinary Medicine; Veterinary Teaching Hospital, University of Milan
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Feline infectious peritonitis (FIP) and coronavirus disease 19 (COVID-19): are they similar?

Running title: Comparison between FIP and COVID-19

Authors: Saverio Paltrinieri [1,2], Alessia Giordano[1,2], Angelica Stranieri[1,2], Stefania Lauzi[1,2]

[1]Department of Veterinary Medicine, University of Milan, Lodi, Italy

[2] Veterinary Teaching Hospital, University of Milan, Lodi, Italy

Corresponding author

Angelica Stranieri[1,2]

[1]Department of Veterinary Medicine, via dell'Università 6, 26900, University of Milan, Lodi, Italy

[2] Veterinary Teaching Hospital, via dell'Università 6, 26900, University of Milan, Lodi, Italy

E-mail: angelica.stranieri@unimi.it

Phone number: +390250334174

Summary

SARS-CoV-2 has radically changed our lives causing hundreds of thousands of victims worldwide and influencing our life style and habits. Feline infectious peritonitis (FIP) is a disease of felids caused by the feline coronaviruses (FCoV). FIP has been considered irremediably deadly until the last few years. Being one of the numerous coronaviruses that are well known in veterinary medicine, information on FCoV could be of interest and might give suggestions on pathogenic aspects of SARS-CoV-2 that are still unclear. The authors of this paper hope to reassume the most important aspects of FIP and COVID-19 and to clear the similarities and differences between these important diseases. SARS-CoV-2 and FCoV are taxonomically distant viruses but recombination events with other coronaviruses are reported for both. SARS-CoV-2 and FCoV differ in terms of some pathogenic, clinical and pathological features. However, some of the pathogenic and immunopathogenic events that are well known in cats FIP seem to be present also in people with COVID-19. Moreover, preventive measures currently recommended to prevent SARS-CoV-2 spreading have been shown to allow eradication of FIP in feline households. Finally, one of the most promising therapeutic compounds against FIP, GS-441524, is the active form of Remdesivir, which is being used as one therapeutic option for COVID-19.

Keywords: feline coronavirus, feline infectious peritonitis, SARS-CoV-2, COVID-19

The current pandemic of coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhou et al., 2020). COVID-19 is now inducing profound changes to our lifestyle and has severe consequences on healthcare systems and finances worldwide. Therefore, a huge research activity on this virus has been developed in the past few months to increase the knowledge on SARS-CoV-2 biology and pathology and to design new strategies for prevention and treatment of COVID-19. Coronaviral diseases are well known in veterinary medicine, since numerous different species of coronaviruses (CoV) affect wild animals (primarily bats or avian species) as well as domestic species such as bovine, swine, feline and canine (Su et al., 2016). Since the late '90s (Paltrinieri et al., 1998), the research activity of our group has been focused on feline coronaviruses and especially on the diagnosis and pathogenesis of feline infectious peritonitis (FIP), a systemic and lethal disease of cats caused by the feline coronavirus (FCoV) (Pedersen, 2009). Therefore, with this review, we want to share our thoughts on the possible similarities and differences between FCoV infection and the preliminary information on SARS-CoV-2 biology and pathology published so far, as an attempt to provide possible points of discussion for future research on human coronaviruses.

Virology

The SARS-CoV-2 belongs to the betacoronavirus genus and to the species Severe acute respiratory syndrome-related coronavirus (Gorbalenya et al., 2020). It is a completely new virus that is thought has originated from recombination events between CoVs of other species, possibly through one or more intermediate hosts. Bats are the most likely candidate reservoir of the SARS-CoV-2 whereas the strong similarities between some pangolin coronaviruses and SARS-CoV-2 in the receptor binding domain (RBD) show that also this species probably played a role in the spillover to humans (Andersen et al., 2020; Lam et al., 2020; Zhang et al., 2020a). Studies are ongoing to identify the possible intermediate hosts (Deng et al., 2020). Recombination is a common behavior for CoVs, that may generate new variants able to infect species other than their natural reservoir (Holmes & Rambaut, 2004). Sequence analysis and phylogenetic studies allowed to identify the recombination events that led to the appearance of new CoV species in

many animal species, and to identify bat coronaviruses as the ancestors of several CoVs of swine, ruminants, birds or rodents (Wong et al., 2019). All these animal species may be affected by different CoV species. Conversely, only 2 types of FCoV, that belongs to the alphacoronavirus genus, are currently known: serotype I and serotype II FCoV. The ancestor of type I FCoV is unknown but alphacoronavirus are known to have likely originated from bats (MacLachlan & Dubovi, 2016). Type II FCoV originated by a double recombination between the FCoV type I and the canine coronavirus (CCoV) (Herrewegh et al., 1998). This recombination moderately influenced the biology of the virus as type II FCoV, compared to FCoV type I, can easily grow in vitro, and it seems to be associated with a different cellular entry pathway. Indeed, types I and II appear to enter the cytosol through late and early endosomes, respectively (Takano et al., 2019a). While the two serotypes show no differences in their pathogenicity, type I FCoV remains the most prevalent strain detected in field cases of FIP (Jaimes & Whittaker, 2018). The SARS-CoV-2 acquired the ability to interact with cellular receptors that allowed to jump from animals to people. Despite recombination events contributed also to the generation of new variants of FCoVs, the number of viral variants in cats is very limited, unlike in other animal species, where several species or strains of species-specific CoVs have been generated, mostly in recent years (Su et al., 2016; Lin et al., 2017). This may depend on the less frequent interaction of FCoVs of pet cats with CoVs of other animal species or on the social/behavioral peculiarities of wild cats that tend to have few interspecific interactions, although wild cats are more exposed to CoVs infecting rodents or birds due to their hunting activity. If this interpretation is correct, the probability of future spillover of CoVs may be reduced by prevention of interspecific interaction of domestic animals and consequently of interspecific exchange of potentially recombining CoVs. Moreover, due to the strict cohabitation between pet cats and people, especially in urban centers, cat infection with the SARS-CoV-2 should be prevented, also in order to avoid possible recombinations. At the moment, there is evidence that SARS-CoV-2 has infected cats in Wuhan, China, as recently showed by positive serological results in a cohort of 15/102 examined cats using ELISA targeting the receptor binding domain (RBD) of the virus (https://promedmail.org/promed-post/?id=7179945). Moreover, SARS-CoV-2 PCR positive results have been recorded in two cats: one cat from Belgium (positive on stool and vomit) and in one cat from Hong Kong (positive on samples from oral and nasal cavities and rectum). Both cats belong

to COVID-19 positive owners. Only the Belgian cat showed mild, respiratory and gastroenteric clinical signs, whereas the other cat was asymptomatic (https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/Belgium_28.03.20.pdf and https://promedmail.org/promed-post/?id=20200402.7173286). More recently, two cats were found positive in the USA, both with mild respiratory symptoms but only one belonging to a COVID-19 positive owner (https://promedmail.org/promed-post/?id=7256272) and one rectal swab from a cat in France also tested positive (https://promedmail.org/promed-post/?id=7289409) . Moreover, lions and tigers seem also to be possibly affected, since cases were recorded in a zoo from New York (https://promedmail.org/promed-post/?id=7266556).

Nonetheless, a former report about the possible susceptibility of cats to the closely related SARS-CoV was published in the early 2000s, with presence of antibodies in asymptomatic infected cats (Martina et al., 2003).

Despite the low frequency of recombination with other CoVs, the FCoV has a high variability in the feline population. The frequency of mutations, especially in some regions of FCoV RNA, is very high and the high replication rate of FCoV in the intestine of affected cats leads to the generation of “quasispecies” in each single cat (Battilani et al., 2003). Some of these new variants may bear mutations that, if coupled with a peculiar immune response of infected cats, are likely to play a key role in the pathogenesis of FIP, as specified below (Pedersen, 2014a).

Phylogenetical analyses of 103 SARS-CoV-2 genomes indicated two major viral types called L (for Leucine) and S (for Serine) that were defined by two single nucleotide polymorphism (SNPs). The S type has been identified as the ancestor type, while the L type seems to have evolved from the S type and is now the most common SARS-CoV-2 type circulating worldwide (about 70%) (Tang et al., 2020). Another study illustrated the presence of two viral clades, genotype I and genotype II, with a higher spreading ability of the second type (Zhang et al., 2020b). Despite whole genome sequence analysis of SARS-CoV-2 showed that the viruses circulating worldwide are almost identical, with a similarity rate of 99.9%, it has been shown that the virus has started to mutate in patients. Mutations mainly occurred in six genes, including S, N, M, ORF8, ORF3a, and ORF1ab (Li et al., 2020a, Shen et al., 2020a, Wang et al., 2020a). Mutations in the S, N, M, ORF7b and

ORF3c are also reported in FCoV and, as below described, have been extensively studied for their possible role in the pathogenesis of FIP (Pedersen, 2014a).

Several variations have been reported to be non-synonymous mutations and reported mutations may affect SARS-CoV-2 virulence, infectivity, and transmissibility (Li et al., 2020a). Based on the high frequency mutations, SARS-CoV-2 genomes have been classified into different groups (Wang et al., 2020b).

It is important to keep in mind that information on genetic heterogeneity of SARS-CoV-2 strains is considered for now not conclusive, but only preliminary and hypothesis-generating (Mavian et al, 2020). However, the hypothesis of the presence of strains with different virulence may justify, along with other epidemiological factors, the variability of clinical signs of COVID-19, that span from mild flu-like symptoms to severe and lethal pneumonia. Further investigations on the genetic diversity of SARS-CoV-2 populations are warranted to support this hypothesis (Chen et al., 2020; Guo et al., 2020; Zhang et al., 2020b).

Epidemiology

Both the SARS-CoV-2 and the FCoV are highly contagious and rapidly spread within susceptible populations. This behavior is typical of many animal CoVs (Guy, 2000; Cavanagh, 2007; Song & Park, 2012; Licitra et al., 2014). When CoVs are introduced into a new population, the infection may show different epidemiological patterns. CoV infection may show an epidemic pattern, as reported with SARS-CoV and currently with SARS-CoV-2. On the other hand, it may become endemic, with a high number of infected asymptomatic individuals and a lower mortality rate, as observed in at least four common human coronaviruses (hCoVs-229E, -NL63, -OC43, and -HKU1) and for almost all the coronaviruses of bats (Vijaykrishna et al., 2007; Corman et al., 2018). An endemic pattern is also observed in cats and FIP. The disease was discovered in the 60s in the US (Holzworth, 1963; Wolfe & Griesemer, 1966) and afterwards likely spread from the US all over the world, when single reports on FIP cases diagnosed in different countries appeared in scientific journals starting from the late 60s-early 70s (Lauzi et al., 2020). In the following years, the number of FIP cases and of FCoV infected cats has been increasing worldwide as such, currently, the rate of FCoV PCR positive and/or seropositive cats in multi-cat environment often approaches 100%. The infection rate has

been reported to increase proportionally with the number of cats per cattery (Pedersen, 2009; Paltrinieri et al., 2014). This high rate of infection, in turn, depends on the only partially protective immunity that cats may mount at the intestinal level. Partial protective immunity allows cats to periodically clear the infection but, once the local immunity decreases, cats can be re-infected if living in FCoV-endemic environments. Therefore, infection develops according to the SIS (susceptible-infected-susceptible) model and most of the cats in FCoV-endemic catteries are recurrent shedders of the virus (Foley et al., 1997), thus contributing to maintain the infection in the environment. Despite this high rate of infection, mortality remains low also due to the peculiar immunopathogenesis of FIP described below (Pedersen, 2014a). Based on the information on the diffusion of COVID-19 from its origin in the Hubei province (China) to the current worldwide distribution, the spread of the SARS-CoV-2 is now in the epidemic/pandemic phase. The efforts of Public Health Authorities are focused on slowing down the infection. It is unlikely that the virus will be eradicated and the infection may enter the endemic phase. In this scenario the risk of additional foci of epidemic infection (as it occurs in cats when FCoVs enter in catteries with low endemicity) may be present, as well as the risk of future mutations of the virus that may modify its virulence.

Pathogenesis, pathology and diagnosis

Although virological and epidemiological aspects of FCoV and SARS-CoV-2 infection have some common features, the pathogenesis of the disease seems to be different. This difference starts at the level of cell entry with the SARS-CoV-2 binding the angiotensin-converting enzyme 2 (ACE2) receptor in humans (South et al., 2020). Predicted homology of feline and human ACE2 receptors (Guo et al., 2008) along with the identification of the same ACE-2 receptor in cats and dogs (Luan et al., 2020) confirms that SARS-CoV-2 infection may occur also in these domestic animals. FCoVs binds receptors different than the ACE-2 receptor in cats. Type II FCoVs employ feline aminopeptidase N (fAPN) as a cellular receptor whereas the receptor used by type I FCoVs is still unknown. However, cell membrane lectins (C-type lectin dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin, fDC-SIGN) seem to play a role in the cell entry for both FCoV serotypes (Regan et al., 2010; Van Hamme et al., 2011).

Moreover, the cellular tropism of the two viruses seems to be partly different. FCoV is a systemic disease affecting different organs, whereas SARS-CoV-2 apparently affects mainly the lungs (Wang et al., 2020c). Nonetheless, neurological and hepatic manifestations have been described in SARS-CoV-2 infected patients and, most importantly, there is growing evidence of gastrointestinal tract involvement (Tian et al., 2020). In several COVID-19 patients, gastrointestinal symptoms have been reported, often before the beginning of respiratory symptoms (Gu et al., 2020). Moreover, PCR on stool samples has been recently recommended and oral-fecal route has been suggested as an additional mode of infection (Cipriano et al., 2020; He et al., 2020). Gastrointestinal involvement was also a characteristic of SARS-CoV, that share the same receptor of SARS-CoV-2 for cellular entry. Indeed, gastrointestinal involvement may be explained by the presence of ACE-2 receptor which are highly expressed in lung epithelial cells as well as in enterocytes from ileum and colon (Zhang et al., 2020c). More recently, SARS-CoV-2 was demonstrated to also been able to actively replicate in human enterocytes *in vitro* (Lamers et al., 2020).

Curiously, enterocytes are the major target of FCoV, although the virulent FCoV strains infect macrophages also. Both type I and type II FCoV, in fact, have 2 distinct pathotypes: one with enteric tropism, formerly known as feline enteric coronavirus (FECV), which may occasionally induce mild gastrointestinal symptoms, and the other, formerly known as feline infectious peritonitis virus (FIPV), which is more able to replicate within macrophages, thus disseminating in the host and inducing FIP. FIP is a systemic disease characterized by granulomatous lesions (“dry” or non-effusive FIP) and/or by vasculitis that induce the development of cavitary effusions (“wet” or effusive FIP). The two pathotypes were for long time considered as distinct viral species, but molecular studies demonstrated that they are two variants of the same virus, with different virulence (Pedersen, 2014a). In turn, the different virulence has been thought to depend on mutations of intestinal strains. However, a single mutation definitely responsible for FIP has not been identified yet, although several candidate genes have been supposed to be involved in this virulence shift (Tekes & Thiel, 2016). Recent studies have identified mutations in the FCoV spike protein as markers of systemic spread of FCoV, regardless of virulence (Porter et al., 2014; Barker et al., 2017). Differences in the nucleotide and amino acid sequence have been reported in the SARS-CoV-2 viral receptor binding domain (RBD) compared

to SARS-CoV. These mutations seem to be associated with an enhanced affinity of the spike protein of SARS-CoV-2 to the ACE-2 receptor, that may explain the higher morbidity of SARS-CoV-2 (Ou et al., 2020; Singh, 2020). The possible role of mutated variants of the SARS-CoV-2 in the pathogenesis of clinical diseases characterized by more severe clinical signs has not yet been fully exploited or elucidated.

While the mutation to the virulent pathotype is the first key event, the second key event in the pathogenesis of FIP is the activation of the immune response. Cats that seem to be more resistant to the infection (i.e. cats that harbor the FCoV in their intestine for months or the recurrent shedders mentioned above) have a very efficient cell-mediated (Th1) immune response. Conversely, the activation of the humoral (Th2) immune response may exacerbate the course of the disease. Antibodies have been shown to accelerate, in vitro, the uptake of the virus by macrophages, according to the mechanism known as "antibody dependent enhancement" (ADE), where anti-FIPV antibodies increase the uptake of FIPV through the macrophage Fc receptor (Olsen et al., 1993). However, the role of ADE was controversial until recently. The first studies on naturally infected cats with repeated exposure to FCoV did not suggest that the presence of antibodies increases the risk of FIP and, at the same time, the high antibody titers of cats that cleared the infection suggested a protective role of antibodies, at least in some cases (Addie et al., 1995). Recently, the role of ADE in disease mechanisms has been confirmed. ADE, in fact, has been documented in experimentally infected cats that were immunized against FIPV and developed FIP, while non immunized cats did not (Takano et al., 2019b).

Interestingly, ADE stimulated by other CoVs is thought to exist for the SARS-CoV-2 and be responsible for the more severe cases recorded in a lower percentage of infected patients, usually among the elderly (Schatzmann Peron & Nakaya, 2020). In particular, this phenomenon could be consequence of the exposure not to SARS-CoV, but to other coronaviruses that cause only mild symptoms and are mistaken for common cold viruses, but allow the host to mount an antibody response (Tetro, 2020). The antibody-dependent infection of macrophages could represent, in fact, a pivotal step towards disease progression from mild to severe symptoms, and may as well explain the dysregulated immune responses in COVID-19, characterized by T cell lymphopenia and proinflammatory cascade with macrophage hyperactivation, both important

known phenomena in FIP (Pedersen, 2014a; Tay et al., 2020). Moreover, progression to the critical phase of the disease often coincides with the beginning of humoral immunity antibody response (Ricke & Malone, 2020). However, even though coronaviruses such as MERS-CoV and FCoV have been demonstrated to actively infect monocytes and macrophages, this needs to be more thoroughly investigated for SARS-CoV-2, also at the light of the fact that ACE-2 is expressed on alveolar macrophages and SARS-CoV-2 can replicate in these latter cells (Pedersen, 2014a; Chu et al., 2020; Kai & Kai, 2020; Ricke & Malone, 2020; Schatzmann Peron & Nakaya, 2020). Moreover, the role of $CD169^{+}$ macrophages in the spreading of SARS-CoV-2 has been recently questioned and needs to be further investigate (Park, 2020). Despite interesting results, the real role of ADE in vivo is still questioned in cats.

Regardless of the ADE mechanism, the role of antibodies in the pathogenesis of FIP has been previously reported by several studies. Indeed, antibodies are known to be involved in the pathogenesis of wet FIP. Intracavitary effusions observed in wet FIP are the consequences of a vasculitis based on the contribution of a type III hypersensitivity reaction, on which immunocomplexes formed by the FCoV and by anti-FCoV antibodies precipitate around the vessel's walls and induce the recruitment of macrophages producing factors. These cytokines damage the tissues and, at the same time, induce the release of neutrophils that intensify the inflammatory process and exacerbate the tissue damage (Acar et al., 2016; Berg et al., 2005; Pedersen, 2009). It is still unclear why only some seropositive cats develop the immune complex disease, while other seropositive cats living in the same cattery do not. Recent studies have observed that serum and tissue patterns of molecules and cells involved in the innate and specific immune response differs in seropositive clinically healthy cats compared with cats with FIP, suggesting that cats may develop or not FIP depending on the type of activation of these responses (Pedersen, 2014a). Some studies suggested that specific sequences of structural proteins of the FCoV may influence the type of immune response mounted by the cat. Therefore, it may be supposed that mutations of the virus may also play a role in the host-virus interactions (Satoh et al., 2010; Rossi et al., 2011; Takano et al., 2014).

The information collected in the few months regarding COVID-19 immune pathogenesis from the first documented cases seems to exclude a direct role of the host's immune response in the development of COVID-19 lesions. Firstly, the median incubation time of the disease (four days in a report of 1099 cases) is

lower than the time required to activate the cells involved in the immune response and the production of antibodies (Guan et al., 2020). Secondly, the administration of neutralizing antibodies containing plasma from patients recovered from COVID-19 seems to be a useful additional therapeutic support for critically ill patients, suggesting that antibodies might have a protective effect against the virus rather than contributing to the development of the disease (Shen et al., 2020b). Thirdly, although mononuclear infiltrates composed by lymphocytes, monocytes and macrophages may be found within COVID-19 lesions, the interstitial pneumonia reported in this disease as well as the presence of syncytial multinucleated cells and pneumocytes showing cytopathic lesions (Felsenstein et al., 2020; Liu et al., 2020; Xu et al., 2020) seems to be directly induced by the replication of the virus within the cells. In particular, the virus infects primarily ACE-2 expressing cells, which are mainly present in the lungs and were demonstrated to be the primary target of the SARS-CoV, with which SARS-CoV-2 share several pathogenic aspects (He et al., 2006; Sarzi-Puttini et al., 2020).

In contrast, FIP lesions are typically characterized by lymphoplasmocytic infiltrates, admixed with activated macrophages and neutrophils and are centered around vessels that show the fibrinoid necrosis typical of immune complex vasculitis (Kipar et al., 2005; Pedersen, 2009). Conversely, in one report only immunostaining for SARS-CoV-2 in lung lesions showed minimal viral protein expression on vessels (Zhang et al., 2020d). However, studies on the possible involvement of the immune system in the development of lesions induced by the SARS-CoV-2 are still scarce. These aspects need to be further exploited through additional studies, also focusing on the possible distribution of viral antigens on tissues other than the lung, or at the light of the recent rising concern regarding atypical COVID-19 manifestations in children resembling Kawasaki disease (Mahase, 2020). In fact, if SARS-CoV and SARS-CoV-2 share similar behaviors, the hyperproduction of inflammatory cytokines from infected cells is probably responsible both for the more severe cases and for the multiorgan involvement (Li et al., 2020b).

Despite the pathogenic differences listed above, the severe acute systemic inflammatory reaction syndrome (SIRS) is common in COVID-19 and in FIP. As above stated, cats may harbor the FCoV without showing clinical signs for years, but when FIP develops the activation of the innate immune response is rapid. The immune response leads to a proinflammatory cytokines overproduction that induces severe

clinical signs such as fever, depression, asthenia, emaciation (Kipar & Meli, 2014) as well laboratory changes such as anemia, lymphopenia, increased serum concentration of globulin fractions and acute phase proteins (Pedersen, 2014b, Stranieri et al., 2018). Fever, fatigue, lymphopenia, increased acute phase proteins have been reported also in COVID-19 (do Nascimiento et al., 2020) and are thought to depend on a "cytokine storm" similar to that reported in FIP cases (Kipar et al., 2006; Dhama et al., 2020; Sarzi-Puttini, 2020). In turn, this cytokine storm may induce a multiorgan failure that is responsible for the high mortality rate of critically ill patients with COVID-19 and this hypothesis is supported by the promising results of immunotherapies with anti-cytokine drugs, especially when using TNF-α blockers (Russell et al., 2020; Sarzi-Puttini, 2020). This type of treatment has never been investigated in cats with FIP, mostly due to cost reasons or to the unavailability of drugs registered for the cat. However, the good clinical response of cats to steroidal anti-inflammatory drugs (Pedersen, 2014b) supports the hypothesis that suppression of the hyperinflammatory response may temporarily improve the clinical condition. This is not completely curative in FIP, due to its peculiar immunopathogenic mechanisms, but it may provide COVID-19 patients with precious time for activating the anti-viral immune reaction or, hopefully, to enhance the effect of antiviral drugs.

Finally, the peculiar FCoV biology and the immunopathogenesis of FIP also affects the possibility to correctly diagnose the disease: ultimately, no molecular or serological tests are able to differentiate virulent and non-virulent strains of FIP (i.e. the former FIPV and FECV). Therefore, PCR or serology may confirm the infection but not the disease. FIP may be erroneously diagnosed in PCR-positive or seropositive cats with non-specific clinical signs such as fever or weight loss due to diseases other than FIP. Conversely, cats with FIP may become PCR-negative or seronegative when immune complexes develop and precipitate in tissues (Pedersen, 1976; Meli et al., 2013). Ultimately, only the detection of the virus in the effusion or within the lesions may confirm the disease, although several clinical or clinico-pathological changes may be highly suggestive of FIP (Stranieri et al., 2018; Tasker, 2018). All these obstacles do not seem to occur in patients affected by COVID-19 since, although asymptomatic SARS-CoV-2 positive patients may be

frequently found (Shi et al., 2020), the diagnosis may be based on PCR positive swabs in patients with clinical signs or with chest diagnostic imaging findings consistent with the disease.

Management and prevention

One anti-FIP/anti-FCoV vaccine has been developed and commercialized, but it is available only in few countries (Fehr et al., 1997). It must be administered to kittens of 16 weeks of age or older, which is several weeks after the maternal protective antibodies decrease, leaving a wide-open time window for FIP manifesting (Addie, 2019). Moreover, the risk of stimulating an excessive antibodies production that, based on the aforementioned ADE occurrence, may induce the disease rather than preventing it, is still debated (Bálint et al., 2014) and the use of anti-FCoV vaccine is not widely diffused so far.

No vaccines have so far been developed to prevent SARS-CoV-2 infection, although several research institutions or pharmaceutical companies are currently working for this purpose. Based on what above stated, the genetic diversity of SARS-CoV-2 strains seems to be lower than that of the FCoV and the humoral immune response seems only partially involved in the pathogenesis of COVID-19. Therefore, vaccination could be a promising preventive tool for this disease, even if the question of whether a certain vaccination regimen could induce long-term protection has been addressed for animal and human coronaviruses (Saif, 2020)

In the absence of an effective vaccine, the major preventive measure adopted worldwide to contain and possibly eradicate the SARS-CoV-2 infection is based on quarantine/isolation of poorly symptomatic infected patients, on confinement measures that limit the circulation of people and on social distancing. Although profoundly affecting our habits, our social life and having a great impact on global economy, so far the application of these measured strongly reduced both the rate of infection and mortality in China and, hopefully, it will reduce the number of infected people worldwide. Such an approach has been already recommended in cats. Years ago, prevention strategies based both on the isolation of shedders until repeated PCR tests on their feces resulted persistently negative and on the early weaning of kittens born

from seropositive or PCR-positive queens have been recommended (Addie & Jarrett, 2001). Although these approaches have been proven to be successful on the management of infection in single catteries, their efficiency has been biased by the lack of common rules imposed to all the cat owners by regulatory bodies (e.g. breed associations, veterinary health authorities). Breeders or shelters managers are usually not willing to apply these strategies. Indeed, the participation to the expected activities of breeding catteries (e.g. mating, participation to cat shows,) or shelters (reintroduction of quarantined cats in larger groups of non-tested animals) inevitably exposes cats to the risk of reinfection and ultimately to the risk of FIP, making almost useless the efforts aimed to make their cats FCoV-negative. This experience reinforces the concept that isolation/quarantine strategies must be applied on a large scale, as Public Authorities are doing in many Countries for COVID-19 and that the application of strict measures only to single districts or cities could become ineffective with time.

Treatment

Although FIP has been historically considered an invariably lethal disease and no successful treatments have been available for decades, effective treatments were recently developed with promising results. Historically, cats with FIP received only supportive or anti-inflammatory treatment, that often ameliorated the quality of life as stated in anecdotal reports, but without clearing from the infection neither stopping the immunopathogenesis of the disease (Addie et al., 2009). This is actually what happens also in COVID-19, where most of the therapeutic efforts to manage sick patients, especially in intensive care units, are based on the management of the acute respiratory distress or on the modulation of the inflammatory reactions, as above mentioned (Alhazzani et al., 2020).

The stimulation of cell-mediated immunity on FIP cats has been proposed in the past and is still one of the most used therapeutic approach. For this purpose, interferon-α or feline recombinant interferon ω, that possess also antiviral properties, are used, even though the efficacy of these treatments is controversial (Pedersen, 2014b; Hartmann, 2017) as it is for polyprenyl immunostimulant (Pedersen, 2014b). The use of interferon for COVID-19 has been questioned mainly for its antiviral activity and, to the authors knowledge,

trials regarding its use in association with other molecules (i.e. antiviral agent ribavirin) are currently ongoing (Lu et al., 2020).

The most relevant changes on the therapeutic approach to FIP cats occurred over the past few years. The peptidomimetic GC-376 and the nucleoside analogue GS-441524, both able to inhibits FCoV replication in different manners, became available and were tested in vitro and in experimental infections (Kim et al., 2016; Murphy et al., 2018), or in cats naturally affected by FIP (Pedersen et al., 2018; Pedersen et al., 2019). More specifically, GC-376 caused disease remission in 35% of the treated cats and it appeared more efficient towards certain clinical presentations of FIP (Pedersen et al., 2018). On the other hand, GS-441524 strongly reduced the viral burden in infected cats and induced the remission of clinical signs after one or more cycles of treatment in the large majority (96.1%) of cats. Despite GS-441524 is not registered for use in cats in many countries, this treatment is now widely diffused among cat owners and breeders that can buy the drug through online distributors. Despite, the use of unlicensed drugs must be abandoned (Letter from Dr. Pedersen, https://sockfip.org/), several anecdotal reports on successfully treated cats are available on on-line blogs. Interestingly, the GS-441524 is the biologically active component of the phosphoramidate prodrug GS-5734 (Remdesivir) that has been tested, with some promising results, also in patients with COVID-19 since its efficacy was previously demonstrated against Ebola and Nipah viruses infections (Cao et al., 2020, Ledford, 2020). Recently, Xraphconn, an orally administered drug containing inotodiol, an anti-inflammatory sterol of fungal origin, has been shown to completely and rapidly clear the virus from the intestine of FCoV infected cats likely by reducing viral replication (Addie et al., 2020). Anecdotal reports on therapeutic successes of this drug in cats with FIP are also published on online blogs. Again, future clinical studies are needed to evaluate the effectiveness of Remdesivir treatment on COVID-19 patients, also considering that the bioavailability of the drug in the lung of COVID-19 patients may differ from that of the intestine or other tissues of cats with FIP.

Conclusive remarks

The FCoV and the SARS-CoV-2 share some common features, such as the rapid spread of the infection within the population, the reduction of the infection rate by isolation of infected patients or the shared

success of similar anti-inflammatory or antiviral compounds. However, FCoV and SARS-CoV-2 differ also in terms of biology of the virus, target cells, pathogenesis and clinical features. Nevertheless, years of studies on FCoV infected cats demonstrate that increasing the knowledge on virus biology and host-virus interactions may improve the chances to contain and, eventually, combat the infection. Moreover, the information gained so far on the aspects of FCoV infection shared with SARS-CoV-2 may serve as a basis for a rapid development of prevention or therapeutic strategies for COVID-19 as well as for studies on the possible interaction between FCoV and SARS-CoV-2, that may occur due to the strict relationship between people and their pet cats.

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None

Conflict of interest

The authors declare that there are no conflict of interests.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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