A Cross-Immunity between SARS-CoV-2 and MERS-CoV: Interest in Anti-SARS-CoV-2 Serotherapy Development Using Dromedary Serum

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ABSTRACT

Backgrounds: A potential cross-immunity between SARS-CoV-2 and MERS-CoV could lead to the development of a serodiagnostic test and/or serotherapy against SARS-CoV-2 using dromedary camel anti MERS-CoV serum.

Materials & Methods: Epidemiological and 66 literature data, of which 35 have been published during 2015-2021, and findings were analysed.

Findings: According to the statistical data reported during COVID-19 pandemic, there are less cases and deaths associated with COVID-19 in countries known for dromedary breeding and the circulation of MERS-CoV (another betacoronavirus disease transmitted by dromedary camels) among humans and dromedaries. This observation and the similarity in genome and immunopathogenicity between SARS-CoV-2 and MERS-CoV, suggest that individuals who have been in contact with MERS-CoV infected dromedaries and/or consumed their products (milk, meat, urine) might have acquired an immunity protecting them against SARS-CoV-2. In addition to neutralizing antibodies, this immunity could also be due to complement proteins, chemokines, and especially antimicrobial peptides (AMP), known for their effect on enveloped viruses.

Conclusion: Most research has focused on vaccines as a solution to stop the pandemic, while serotherapy hasn't significantly aroused the interest of researchers. This potential cross-immunity between SARS-CoV-2 and MERS-CoV could lead to the development of a serodiagnostic test and/or serotherapy against SARS-CoV-2 using dromedary camel anti MERS-CoV serum.

Keywords: SARS-CoV-2, MERS-CoV, Cross-immunity, Serotherapy.

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Introduction

Cross-immunity is described as an acquired immunity against an infectious agent (virus or bacteria), which could also protect against another agent. Cross-immunity is related to the cross-reaction phenomenon. In general, each antibody is specific for one antigen but sometimes, some antibodies could link to other antigens with the same epitopes or similar structure, which suggests that cross-immunity could exist between microorganisms, especially those belonging to close families. This phenomenon is observed among some *Salmonella* species, for example, between *Eberth bacillus* and *S. paratyphi* A. In viruses, there is a cross-immunity between different strains of influenza virus due to Hemagglutinins (H) and Neuraminidases (N). Those individuals exposed to a viral strain with a determined H (or N) could be protected against another strain with a similar H (or N) [1-2].

During the COVID-19 pandemic, researchers and healthcare professionals have talk a lot about vaccine but a little about serotherapy. Based on the cross-reactivity phenomenon, serotherapy could be a proper solution for many infectious diseases, especially viral infections. Serotherapy consists of the treatment via the administration of neutralizing antibodies recovered from the sera of infected and then cured individuals [3-4]. Influenza viruses [5-6], RSV [7-8], and HIV [9-10] are among the viruses mostly screened for antiviral serotherapy.

Objectives: This article sought to demonstrate through observations, literature data, and data analysis that a potential cross-immunity between SARS-CoV-2 and MERS-CoV could lead to the development of serotherapy against COVID-19 using dromedary serum. This cross-reaction could also be used to develop a serodiagnostic test of SARS-CoV-2, using dromedary serum to detect SARS-CoV-2 antigens.

Observation: Less COVID-19 cases and deaths are reported in countries with dromedary breeding

Middle East respiratory syndrome coronavirus (MERS-CoV) disease is a viral infection transmitted to humans through infected dromedaries [11-12]. The first MERS-CoV cases appeared in 2012 in Saudi Arabia [13-14]. According to WHO, 2468 MERS-CoV confirmed cases and 850 deaths were reported in 27 countries during 2012-2019 [15-16]. It has been reported that this betacoronavirus is a zoonotic virus among dromedaries in the Middle East (especially in Arabian Peninsula), Pakistan, Bangladesh, as well as many African countries like Morocco, Ethiopia, Sudan, etc. [17-18].

According to the COVID-19 pandemic statistics until March 03, 2021, it could be observed that there is a remarkable difference in the total numbers of infected cases and deaths between countries with MERS-CoV circulation, due to dromedary breeding, and other countries with no dromedary breeding and therefore no MERS-CoV circulation. Table 1 represents some data showing this difference between three categories of countries. The countries in each category were chosen according to the presence or absence of dromedary breeding practice and MERS-CoV as well as the prevalence of MERS-CoV in humans. The list of countries in each category could be extended, but this will not have a significant impact on the results. Three categories are as follows:

- Category 1: Countries with no dromedary breeding and no MERS-CoV circulation (Germany, UK, France, Spain, and Italy)-
- Category 2: Countries with dromedary breeding and high prevalence of MERS-CoV in humans and dromedaries (Saoudi Arabia, UAE, Qatar, Oman, and Jordan)
- Category 3: Countries with dromedary breeding and moderate to low prevalence

of MERS-CoV in humans (constituted essentially of African countries, including Morocco, Kenya, Ethiopia, Nigeria, and Burkina Faso)

In countries in Category 1, it could be observed that the total numbers of infected cases and deaths due to COVID-19 were high, while these two parameters were low in Categories 2 and 3. In Category 1 countries, the total number of infected cases ranged from 2.49 M (million) in Germany to 4.19 M in the UK, while the total number of confirmed cases ranged from 143000 (in Oman) to 408000 (in Jordan) in Category 2 as well as from 12071 (in Burkina Faso) to 485000 (in Morocco) in Category 3. Concerning total number of deaths, these values were

around 70247 to 124000 (Spain/UK), 260 to 6510 (Qatar/Saudi Arabia), and 153 to 8653 (Burkina Faso/Morocco) in Category 1, 2, and 3 countries, respectively. Since the total number of reported cases may be influenced by the screening capacity of each country, the D/C ratio (total deaths/ total cases) was calculated in percent (%) to confirm observations. D/C values ranged from 2.23 to 3.31 (Spain/Italy), 0.15 to 1.72 (Qatar/Saudi Arabia), and 1.23 to 1.78 (Nigeria/Morocco) in Category 1, 2, and 3 countries, respectively. The obtained D/C values showed that COVID-19 caused more mortality in Category 1 countries compared to the other categories. Furthermore, the difference observed between the Categories 1 and 3 would have been much higher if

Table 1) Distribution of the total number of infected cases and deaths due to COVID-19 in the three categories of countries until March 03, 2021 [19-20].

| Countries	Total Cases	Total Deaths	Total Cases/1M Pop	Recovered	Total Deaths/Cases (in %)
Germany	2.49 M	71 852	87553	2.32M	2.88
UK	4.19M	124 000	62865	3.14M	2.95
Spain	3.14M	70247	66808	2.74M	2.23
France	3.81M	87542	56865	263 500	2.29
Italy	2.98M	98635	49370	2.44M	3.31
Saudi Arabia	378K	6510	11030	369K	1.72
Qatar	165K	260	71120	155K	0.15
Jordan	408K	4793	40396	356K	1.17
Oman	143K	1583	28600	133K	1.1
UAE	399K	1269	40937	386K	0.31
Morocco	485K	8653	13298	470K	1.78
Kenya	107K	1866	2035	86914	1.74
Ethiopia	162K	2391	1441	136K	1.47
Nigeria	157K	1939	781	137K	1.23
Burkina Faso	12071	153	595	11657	1.26

Table 2) Distribution of COVID-19 cases in different regions of Morocco until March 03, 2021 [21].

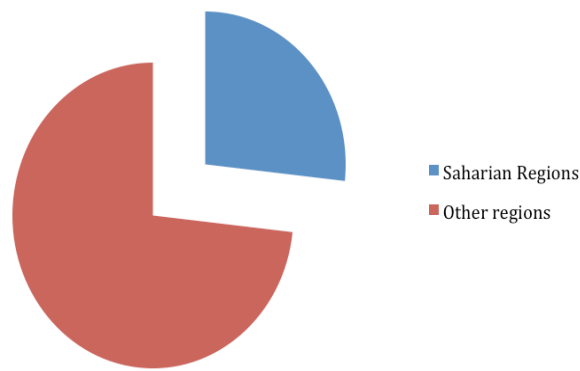| Regions	Total Cases	Total Cases/1M Pop
Casablanca-Settat	129 300	18805
Rabat-Sale Kenitra	51 970	10801
Tanger-tetouan	118 855	33142
Marrakech-Safi	80 265	15952
Fes-Meknes	78 400	18280
Beni Mellal-Khenifra	3381	1250
Oriental	7590	2889
Deraa-Tafilalt	9 590	8230
Souss-Massa	2652	703
Guelmim-Oued Noun	1067	2464
Dakhla-Ouad Dahab	970	6736
Laayoune-Sakya El Hamra	1311	4189
Total	485353	

all countries had the same level of health services. In fact, D/C values would have been considerably higher in Category 1 and much lower in Category 3.

In order to provide more evidence supporting our hypothesis, the statistics of Morocco were analysed as it's a country where two regional categories were found: Saharian regions with dromedary breeding (Dakhla, Laayoune, and Guelmim) and regions without dromedary breeding (the other 9 regions of Morocco). The results summarized in Table 2 show a clear difference in the total number of COVID-19 confirmed cases between the two regional categories. In fact, total cases were 970, 1067, and 1552 cases in Dakhla-Ouad Dahab, Guelmim-Oued Noun, and Laayoune-Sakya El Hamra, respectively. By comparing Saharian regions to the other regions of Morocco, it was found that only 0.69 % of cases were related to Saharian

regions, while 99.31 % were related to the other regions (Figure 1). Also, there was only 4463 cases/ 1M Pop in Saharian regions, whereas this parameter increased to 11313 in the other regions (Figure 2).
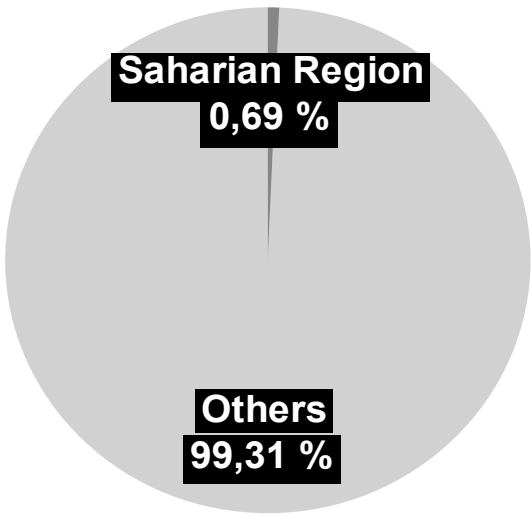
Figure 1) Distribution of COVID-19 total cases in Saharian regions and other regions of Morocco

Figure 2) Total cases / 1M Pop in Saharian regions and other regions of Morocco

Similarity between SARS-CoV-2 and MERS-CoV pathogenicity

SARS-CoV-2 and MERS-CoV have the same pathogenic effect since they both cause severe respiratory syndrome in human by infecting lower respiratory tract [22-23]. Compared to MERS-CoV and SARS-CoV, it seems that SARS-CoV-2 infection is characterised by milder symptoms [24]. Other betacoronaviruses cause infections with different symptoms. In fact, Bovine CoV/ENT with cow as its host causes diarrhea, and Equine CoV/Obihiro12-1 with horse as its host, causes fever, anorexia, and leukopenia [25]. In addition to respiratory symptoms (cough, sore throat, and shortness of breath), fever and fatigue are the most common symptoms associated with SARS-CoV-2 and MERS-CoV infections. Diarrhea is rarely reported [26-28]. On the other hand, it has been reported that lymphopenia and "cytokine storm" of pro-inflammatory cytokines (IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα) may play an important role in SARS-CoV-2 and MERS-CoV immunopathogenicity [29-30]. This "cytokine storm" could lead to complications such as pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, and potentially death [31].

SARS-CoV-2 genome is similar to that of MERS-CoV

The genome of coronaviruses is a +ssRNA (single-stranded positive-sense RNA). Its size is about 30kb, the largest genome among RNA viruses, with a 5′-cap structure and a 3′-poly-A tail. The 3′- terminus part of this genome encodes four main structural proteins, including spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Other parts of the genome encode many non-structural proteins (nsp). Most of these nsps are responsible for the virus replication [32-33]. Comparing different coronavirus genomes, it has been reported that there is 54 % identity in the whole genome (58% in the nsp-coding region and 43% in the structural protein-coding region) between SARS-CoV-2 and MERS-CoV genomes [24, 34-35].

SARS-CoV-2 and MERS-CoV immunity: Importance of S-protein as an inducer of immune response

In viral infections, innate immune response is mostly based on the type 1 interferon (IFN-1) cascade that controls viral replication and subsequently induces adaptive immune responses. Clinical and experimental data as well as similarity between SARS-CoV-2 and MERS-CoV genomes led us to hypothesize that the host immune system may evade and response similarly to the infections caused by these two viruses. It has been reported that progression and severity of both SARS-CoV-2 and MERS-CoV infections, are characterized by an early high serum levels of pro-inflammatory cytokines (IP-10, MCP-1, MIP-1A, and TNFα.2) [27]. This finding suggests that there might be a similar cytokine storm-mediated disease severity induced by these two viruses [30, 35]. Also, increased monocyte/macrophages have been observed in severe cases of both COVID-19 and MERS-CoV infections [36-37]. Humoral immunity is mediated by the secretion of substances in the blood or body fluids, such as antibodies, complement proteins, and certain antimicrobial peptides. In SARS-CoV-2 and MERS-CoV, immune

Table 3) Comparison of genome and protein structure between SARS-CoV-2 and MERS-CoV (AA: Amino Acid, nsp: non structural protein)

	SARS-CoV-2	MERS-CoV
Lengths	29 Kb	30 Kb
Open reading frames	11	11
Structural proteins	4	4
Non structural proteins	> 5	16
Spike protein	1274 AA (S1: 936)	1353 AA (S1: 1010)
M protein	223 AA	220 AA
E protein	76 AA	83 AA
N protein	420 AA	414 AA
Some non-structural proteins	nsp 1: 181 AA	181 AA
	nsp 3: 1362 AA	1361 AA
	nps 5: 306 AA	305 AA
	nsp 7: 84 AA	84 AA
	nps 11: 14 AA	14 AA
	nsp 12: 932 AA	933 AA

cells (T and B) epitopes are built for the main four structural proteins S, N, M and E of the virus. Neutralizing antibodies limit viral infection by their protective effect and prevent the possible reinfection in the future [38]. Seroconversion occurs 4 days and 2-3 weeks after the onset of COVID-19 and MERS-CoV infections, respectively. In SARS-CoV infection, neutralizing antibodies are found up to two years after infection [39]. For MERS-CoV, antibodies persist for at least one year [40]. In coronavirus infections, severe outcomes could be related to delayed and weak antibody responses [38].

It has been reported that most antigenic peptides are found in the structural proteins, especially spike protein [41], which means that spike protein (S) is not only responsible for receptor binding and membrane fusion of the virus to host cells [42], but also plays a major role in both humoral and cellular immunity [43]. Since it's considered as the principal antigenic molecule, spike protein is used as a significant target for the development of vaccine. In fact, infection of Vero E6 cells by some SARS-CoV strains was shown in a study to be neutralized by anti-S1 antibodies (amino acids 485-625) [44-45]. In another study, a DNA vaccine encoding full S protein of SARS-CoV U was shown to induce neutralizing antibodies and T-cell responses [46]. On the other hand, several vaccines targeting S protein have been developed against MERS-CoV, and it has been reported that RBD (receptor-binding domain) region of S protein induces the highest level of IgG antibodies in mice [47]. Also, a DNA vaccine encoding subunit S1 of MERS-CoV spike protein was shown to induce humoral and cellular immune response in mice [48]. Cameron et al. (2007) reported that infected patients with fatal outcomes had a deficient

antibody production against S protein [49]. Clustering regions of B-lymphocyte and CTL epitopes in N and M proteins were also shown to induce antibody and T-cell responses in humans [50-54].

Potential cross-reactivity between SARS-CoV-2 and MERS-CoV

Despite the similarity observed between antigenic peptides of SARS-CoV-2 and MERS-CoV, researchers do not agree regarding the presence of a potential cross-immunity between these two viruses. In fact, some authors have reported the absence of cross-reactivity between SARS-CoV-2 and MERS-CoV [55-58]. Du et al. (2013) showed that monoclonal antibodies specific to SARS-CoV RBD and serum polyclonal antibodies specific to SARS-CoV S-RBD didn't cross-react with or neutralize MERS-CoV [58]. However, another study on the structure of S2 region of spike protein of MERS-CoV and SARS-CoV, suggests that a T-cell cross reactivity might exist between MERS-CoV and SARS-CoV [38].

Sequence analysis of the four structural proteins (especially Spike protein) shows the conservation of antigenic peptides in SARS-CoV and MERS-CoV S, N, M and E proteins, suggesting that cross-immunity could be possible between SARS-CoV-2 and MERS-CoV since S-protein is considered as the most antigenic component of coronaviruses [38, 44-45]. Table 3 summarizes some similarities between genomes and proteins of SARS-CoV-2 and MERS-CoV.

Hypothesis

According to the statistical data reported during COVID-19 pandemic, there are less cases and deaths associated with COVID-19 in countries known for dromedary breeding practice (especially in Middle East and Africa). These countries are also known for the circulation of MERS-CoV (another betacoronavirus transmitted by dromedary

camels) among humans and dromedaries. This findings and the similarity of genomes, antigenic peptides, and immunopathology of SARS-CoV-2 and MERS-CoV lead us to think that there is a potential cross-immunity between SARS-CoV-2 and MERS-CoV. Individuals from countries with dromedary breeding might have acquired immunity due to their contact with dromedaries, which protects them against SARS-CoV-2. A study performed in these countries reported that individuals with direct and indirect contact with dromedaries (Slaughterhouse worker, camel herders, etc.) and individuals consuming dromedary products (Milk, meat, and urine) had higher seropositivity rates for MERS-CoV compared to general population [17, 59-60].

The interest in investigating this potential cross-immunity between SARS-CoV-2 and MERS-CoV is due to the possibility of developing an anti-SARS-CoV-2 serotherapy using dromedary serum [61]. In fact, most studies targeting cross-immunity and serotherapy have been done on human or mouse sera, not on dromedary serum [28, 55-58]. Many neutralizing monoclonal antibodies (mAbs) targeting SARS-CoV spike protein have been reported to be produced in mouse [45] or human sera [62-63]. Therapeutic approach based on anti-MERS-CoV neutralizing mAbs has been developed but not approved for commercial use [64-65].

Another interesting point about our hypothesis is the possible presence of other innate immune effectors such as complement proteins, chemokines, and especially AMPs (antimicrobial peptides) in dromedary serum, which are known for their effect not only on bacteria and fungi but also on enveloped viruses like coronaviruses [66].

Conclusion

In addition to vaccination, serotherapy could also play an important role against

viral infections. Since a potential cross-immunity could exist between SARS-CoV-2 and MERS-CoV, there is a hope to develop a serotherapy using dromedary serum to fight COVID-19. Also, the same serum may contain other innate immune effectors such as complement proteins, chemokines, and antimicrobial peptides, which are effective against enveloped viruses like SARS-CoV-2.

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