COVID-19: The Immune Responses and Immunotherapy

Najlaa ASSAID and M’hammed SARIH*

Laboratoire des Maladies Vectorielles (LMV), Institut Pasteur du Maroc, 1 Place Louis Pasteur, 20100 Casablanca, Morocco.

*Corresponding Author : Dr. M’hammed Sarih
Laboratoire des Maladies Vectorielles (LMV), Institut Pasteur du Moroc, Casablanca, Morocco
mhammed.sarih@pasteur.ma

SUMMARY
The protective role of the host’s immune response during SARS-CoV2 infection has become a critical issue in the absence of specific treatment, preventive vaccine, or immunotherapy. During SARS-CoV-2 infection, the immune response would contribute to the host’s defense in the majority of cases, but is responsible for its pathogenesis in some patients. Thus, a better understanding of the immune response during human infection with Sars-cov-19 is important to optimize therapeutic and vaccine strategies. In this review, we summarize the current state of knowledge about the innate and adaptive immune responses elicited by SARSCoV-2 infection, the immune pathways that likely contribute to disease severity and death, and clinical trials for treatment of Covid-19 by immunotherapy.

1. Introduction
The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly spread around the world and has caused major socio-economic damage (Huang et al., 2020). This virus causes coronavirus disease 2019 (COVID-19) which can present with symptoms ranging from mild respiratory symptoms to acute respiratory distress syndrome (ARDS)(N. Chen et al., 2020). Increasing evidence shows that dysfunction of the immune response is closely associated with disease progression in patients infected with viruses (Cui et al., 2003). During 2 to 14 days of infection, symptoms appear and the risk of contagion and nosocomial transmission sets in. Then the virus moves with its humoral component and its cellular component, the immune response against a virus results in its elimination and recovery. However, in some cases of covid 19, this response becomes an aggravating factor (D. Li et al., 2020; Tan et al., 2020) and is responsible for intense inflammation and alterations which go beyond
those produced by the virus itself. In severe forms, an imbalance between the protective immune response and inflammation could be fatal. Thus, many questions arise about the generation of specific immunity against the various proteins of the virus, the kinetics, the function of the antibodies, as well as the quality of the responses of the cluster of differentiation CD4+ and CD8+ effector lymphocytes for the host protection. The bioinformatics study of the T and B epitopes of coronaviruses has raised the question of cross-immunity between SARS-COV-2 and other coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV (Grifoni et al., 2020a). Some affected patients hyperinflammation associated with a "cytokine storm" (Mehta et al., 2020). Although the underlying mechanisms are still poorly understood, escape from innate immune mechanisms by coronaviruses could play an important role. Understanding the immunopathology of COVID-19 should help to define precision medicine for treating COVID-19 patients based on predictive biomarkers of severity. In this review, we take stock of the innate and adaptive immune responses during Covid-19 and their potential roles in the protection and pathogenesis of infected people, as well as the different clinical trials of immunotherapy for the treatment of Covid-19.

1. Innate immunity

Innate immunity plays a key role in the early stages of infection with intracellular bacteria and viruses. Infected lung epithelial cells by sars-cov-2 produce inflammatory mediators like interleukins (IL-6, IL-1b) and interferons IFN-I (IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω). This induces recruitment of monocytes, granulocytes and lymphocytes from the circulation. Sustained production of IL-6 and TNF-α (tumor necrosis factor α) by monocytes can lead to several cascades of hyper-inflammation. Inflammatory macrophages derived from monocytes can enhance the inflammatory response. Other myeloid cells, such as dendritic cells, are believed to have an IFN-dependent role in viral control. Other chemokines produced by monocytes such as CXCL9/10/11 could recruit natural killer cells (NK) from blood (Figure 1). Several studies have reported a quantitative and qualitative reduction of peripheral blood NK cells from COVID-19 patients, which is associated with disease severity (Song et al., 2020; W. Wang et al., 2020). The majority of lung NK cells are non-resident (Gasteiger et al., 2015; Marquardt et al., 2017) and the Chemokine receptor CXCR3 has been shown to induce recruitment of NK cells from peripheral blood to the lungs in COVID-19 patients. NK cells express inhibitory and activating receptors which regulate their cytotoxicity. They are therefore capable of inducing lysis of cells infected with the virus. In addition, the secretion of immunoglobulin IgG1 and IgG3 during infection with SARS-CoV-2 (Amanat et al., 2020) can induce the activation of NK cells via the the crystallizable fragment (Fc) by the recognition of antibodies either linked to surface antigens expressed on infected cells, or to extracellular virions such as immune complexes (Figure 1). This interaction could trigger both cytokine production by NK cells and lysis of infected cells by antibody-mediated cellular cytotoxicity (ADCC). These results suggest that triggering NK cell activation may not only contribute to the resolution of infection, but also contribute to the cytokine storm in ARDS. Significantly elevated systemic levels of pro-inflammatory cytokine IL6 have been reported in several COVID-19 patient cohorts and correlate with disease severity (Mehta et al., 2020). IFN-I is a first line of defense during viral infection, that disseminate in the absence of this cytokine (Liu et al., 2012). A defect in the production of IFN-I triggers an alteration in adaptive immune responses. It has been described that a decrease in the production of type I IFNs in some patients due to genetic abnormalities (3-4% of
severe forms) (Bastard et al., 2020). L'IFN-α / β plays a crucial role in antiviral immunity by inducing the expression of genes (interferon-stimulated genes) which code several factors involved in the inhibition of different stages of the viral cycle, and thus allow the establishment of a state of resistance to viral infections (Liu et al., 2012). Our current knowledge of interactions between SARS-CoV-2 and the immune system is limited. Nevertheless, the virus probably uses some escape mechanisms common to the Coronavirus family in order to replicate more efficiently. Altered IFN-α / β response has been associated with Covid-19 infections (Hadjadj et al., 2020). Patients with low plasma level of IFN-α / β had a high blood viral load, an exacerbated inflammatory response, and increased levels of TNF-α and IL6 (Hadjadj et al., 2020). Comorbidities such as obesity can inhibit the production of type I IFN (Honce et al., 2020; Terán-Cabanillas and Hernández, 2017). Finally, genetic factors can influence the response of IFN and explain the inter-individual variability of the antiviral response. In addition, administration of type I IFN would have reduced the duration of virus detectable in the upper respiratory tract, correlating with reduced blood levels for IL-6 and inflammatory C-reactive protein (CRP).

In addition to IFN-I, we note the involvement of the production of cytokines and chemokines such as IL-1, IL-6, IL-8 or the chemokine ligand CXCL10 in the severity disease and mortality (Blanco-Melo et al., 2020). Much like SARS or MERS, severe forms of COVID-19 are associated with hyperinflammatory status with elevated serum and alveolar concentrations of many inflammatory cytokines including interleukin IL-2, IL-6, IL-10 and TNF-α as well as chemokines CCL2, CCL3 and CCL10 (Vabret et al., 2020). As in SARS, this "cytokine storm" explains a deterioration in the condition of some patients after 7-10 days despite a drop in viral load (J. Chen et al., 2020). The study of murine models and samples (bronchoalveolar lavage (BAL) and blood) from severely affected patients suggests a primordial role of pulmonary and extrapulmonary macrophages, capable of secreting large quantities of IL-6, TNF-α and CCL2 (Diao et al., 2020; Wan et al., 2020).

On the other hand, it has been described that unconventional T lymphocytes (mucosal associated invariant T cells (MAIT), γδT, and natural killer T cells (NKT)) in the respiratory tract of severe COVID-19 patients have a phenotype altered and highly activated, suggesting a potential contribution to the regulation of local inflammation. Also, expression of the activation marker CD69 on NKT and on MAIT of COVID-19 patients were predictive of the clinical course and severity of disease (Jouan et al., 2020).
Figure 1. Infection with SARS-CoV-2 leads to activation of myeloid cells and changes in NK cell function. IL-6, IL-1b and IFN-I / III from infected lung epithelial cells can induce inflammatory reactions by recruiting monocytes, granulocytes and lymphocytes from the circulation. Sustained production of IL-6 and TNF-α by monocytes can lead to several cascades of hyper-inflammation. Inflammatory macrophages derived from monocytes can enhance the inflammatory response by secreting inflammation mediators. Other myeloid cells, such as dendritic cells, are believed to have an IFN-dependent role in viral control. Other chemokines produced by monocytes such as CXCL9 / 10/11 could recruit NK cells from peripheral blood (Vabret et al., 2020).

2. Adaptive immunity

The adaptive immune response consists of three components: the production of antibodies by B lymphocytes (humoral immunity) and the response of CD4 + lymphocytes and CD8 + lymphocytes (cellular immunity).

1.1 Humoral immunity

The main characteristics of the humoral response against SARS-CoV-2: i) Seroconversion begins on the sixth day after the onset of symptoms and reaches a maximum during the second week. ii) The seroprevalence in patients infected with sars cov-2 is heterogeneous and varied from 47 to 100%, depending on the tests and target populations (Lou et al., 2020; Okba et al., 2020), iii) Several studies have found that early and high levels of anti-SARS-CoV-2 antibodies are associated with serious illness (EDOUARD et al., 2020; Yongchen et al., 2020).

The quality of antibodies production is crucial for long-term immunization against harmful viruses. A study of antibody responses to SARS-CoV-2 in patients with COVID-19 showed that almost all patients developed specific antibodies to the virus within 2 to 3 weeks after onset of symptoms (Huang et al., 2020). The importance of these aspects is crucial for the serological diagnosis of COVID-19. The receptor binding domain (RBD) of the angiotensin converting enzyme receptor (ACE2) is the main target of antibodies neutralizing SARS-CoV-2 (Vabret et al., 2020). The measure of the neutralizing capacity of immunoglobins IgG, IgM and IgA anti sars-cov-2 was performed in acute and convalescent patients.
using the different antigens of sars-cov-2. Most acute and convalescent COVID-19 subjects have been shown to have detectable circulating antibodies to SARS-CoV-2 RBD, S, and N, as well as neutralizing antibodies. The impact of these antibodies in the acute phase of the disease is still poorly understood and the first published results are contradictory. Although in the vast majority of cases these antibodies aid the immune response, certain immunoglobulins may promote the penetration of viruses into immune cells leading to their activation, via a phenomenon called antibody dependent enhancement (Casadevall and Pirofski, 2020). There is some evidence that this phenomenon played a role during the SARS epidemic in 2003, during which significantly higher levels of anti-S antibodies in deceased patients were observed. It has been described that the antibody titers as well as the titers of neutralizing antibodies are significantly higher in patients with severe form of SARS cov2 (Vabret et al., 2020). The same study showed that patients with high B cell levels have poor survival (Vabret et al., 2020). The protection conferred by (or even the possible deleterious role) these antibodies, as well as their persistence via memory B lymphocytes during infection by Coronavirus, remains to be known.

Figure 2. Antibody mediated immunity in SARS-CoV-2 Anti sars-cov-2 IgM and IgG antibodies are detected in sera between 7 and 14 days after the onset of symptoms. Viral ribonucleic acid (RNA) is inversely correlated with titers of neutralizing antibodies. Higher titers have been observed in critically ill patients, but it is unknown whether the antibody responses in any way contribute to the pulmonary pathology (Vabret et al. 2020).

1.2 Cellular immunity

Lymphocytes can roughly be divided into CD4 + helper T cells regulating the response of other immune cells, cytotoxic CD8 + T cells involved in the destruction of infected cells, and antibody-producing B cells. An effective immune response against viral infections depends on the activation of cytotoxic T cells that can clear infection by killing virus-infected cells. Lymphocytes T participate in
the adaptive immune response. Unlike the innate immune response, this second phase of the immune response is called specific, based on the recognition and memorization of pathogens. The study published in the journal "Cell" indicates that anyone with Covid-19 - even those with mild or asymptomatic cases - develops "memory T lymphocytes". It has been described that Sars-CoV-2 causes the production of robust, large and highly functional 'memory T cells (Grifoni et al., 2020b). Other recent studies support this discovery (Schlom and Donahue, 2020; Weiskopf et al., 2020). During SARS-CoV-2 infection, the reactivity of T lymphocytes appears to be decisive for the course of the disease. They play a crucial role in upgrading all the specific mechanisms that work to eliminate the virus.

Moderbacher and its collaborators examined relationships between COVID-19 disease severity and the three components of adaptative immunity: neutralizing antibodies, SARS-CoV-2-specific CD4+ T cells, or SARS-CoV-2-specific CD8+. They found that the presence of neutralizing antibodies was not associated with a decrease in the severity of the disease. In contrast, SARS-CoV-2 specific CD4 + T and CD8 + T lymphocytes were significantly associated with less severe disease. They identified a case of COVID-19 without detectable neutralizing antibodies and which resolved the infection without hospitalization. This individual had CD4 + and CD8 + T cells specific for SARS-CoV-2, suggesting an ability of T cell-mediated immunity to control infection (Moderbacher et al., 2020).

If the implementation of the immune response is late and its adaptation and level insufficient, the virus will not be eliminated and may cause significant damage. If, on the contrary, the response is in excess, it is the defense mechanisms themselves which will aggravate the pathology. A good T-response specific to SARS-CoV-2 can predict a favorable course of the infection. They consider that the loss of efficiency of this cellular response that accompanies aging could explain the frequent severity of covid-19 in the elderly. Immunopathogenesis in COVID-19 is a serious problem (Cao, 2020). An early and effective cellular immune response against conv-19 depends on the innate immune response. The dysfunction of innate immunity results in a failure of the response of CD4 + and CD8 lymphocytes. This could be due to an abnormality in the function of the antigen-presenting myeloid cells or their availability in the elderly (Zhao et al., 2011). It is possible that late T cell responses may amplify the inflammatory process in the presence of high and sustained viral loads in the lungs, through multiple possible mechanisms (Li et al., 2008; Liu et al., 2019).

The majority of patients with COVID-19 present with lymphopenia (Chen et al., 2019; Huang et al., 2020) related to the severity of the pathology. However, the factors which might cause the lymphopenia in COVID-19 patients, not yet elucidated. Flow cytometric analysis of patients with COVID-19 shows a decrease in lymphocytes CD4+ and CD8+ (Weiskopf et al., 2020) in the blood and bronchoalveolar lavage (BAL) in the most severe patients (Liao et al., 2020). Still poorly understood, the mechanisms of this lymphopenia could involve (a) a production deficit by medullary sideration, (b) a grouping of lymphocytes within the affected organs or lymphoid organs and / or (c) destruction of these cells by apoptosis, direct cytotoxic effect of the virus or by intramedullary or peripheral hemophagocytosis. Finally, T lymphocytes from severely affected patients express more activation markers and also have less intracellular labeling for interferon-γ, granzyme B or TNF-α (Grifoni et al., 2020b). It has been described that a coordinated response of CD4 + T cells, CD8 + T cells and antibodies has a protective effect. However, an uncoordinated response often fails to control the disease. The severity of illness in the elderly may be explained by the presence of an altered adaptive immune response to...
SARS-CoV-2 (Moderbacher et al., 2020). The production of cytokines and chemokines such as IL-1, IL-6, IL-8 or the chemokine ligand CXCL10 are implicated in the severity of the disease. CXCL10 has been shown to have no correlation with antibody titers, but it has a strong negative correlation with most features of CD4+ and CD8+ T cells specific for SARS-CoV-2. Thus, CXCL10 is a good marker diagnosis of poor response of SARS-CoV-2 specific CD4+ and CD8+ T cells in patients with acute COVID-19 (Moderbacher et al., 2020).

2. Cross immunity

Another immunity could have a significant influence on susceptibility to the disease: so-called "cross" immunity. Indeed, several studies suggest that acquired immunity against the coronaviruses that cause common colds may help patients infected with SARS-CoV-2 fight the virus. Alba Grifoni and his colleagues have thus detected CD4+ T lymphocytes which reacted to SARS-CoV-2 in around 20 people who had never been in contact with the virus. Likewise, Julian Braun and colleagues observed that some healthy people carried CD4+ T lymphocytes in their blood capable of recognizing the virus (Braun et al., 2020). The researchers found, not only in 83% of the 18 patients with Covid-19 they examined, but also in 34% of 68 healthy blood donors, CD4+ T lymphocytes capable of recognizing the S protein of the virus (Braun et al., 2020).

Other teams have examined whether the antibodies of a patient who had been infected with SARS-CoV in 2003 reacted to other coronaviruses, including SARS-CoV-2. One of these antibodies, S309, showed a particular affinity for the S protein of SARS-CoV-2 (Pinto et al., 2020).

3. Immunotherapy

3.1 Treatment with cytokines

Early application of IFN-β to mice infected with MERS-CoV has been described to have a beneficial effect and protect the lung from infectin. On the other hand, late administration has a detrimental effect by increasing the production of damaging pro-inflammatory cytokines (Channappanavar et al., 2019). Clinical trials conducted on the use of IFN-I with or without antiviral remain inconclusive. To date, combined therapy between IFN and anti-virals should be used with caution with COVID-19 infection.

Following preliminary reports of IL-6 as a critical cytokine in cytokine release syndrome (SLS) associated with COVID-19, monoclonal antibodies that target the IL-6 signaling pathway have been identified. They tested as therapeutic candidates (Moore and June, 2020)(Figure 3). The commercial anti-IL-6R antibodies tocilizumab (Actemra) and sarilumab (Kevzara) and the anti-IL-6 antibody siltuximab (Sylvant) are currently being tested for their efficacy in the management of Cytokine Release Syndrome (CRS) linked to Covid-19 and pneumonia in 13 ongoing clinical trials (Table 2). To date, only one group has reported preliminary results from a cohort of 20 COVID-19 patients treated with a single administration of anti IL-6R (400 mg, iv), along with lopinavir, methylprednisolone, and oxygen therapy. (ChiCTR2000029765) (Xu et al., 2020). In addition to the IL-6 signaling pathway, other elements associated with cytokines and chemokines, including IL-1R, GM-CSF and the chemokine receptor CCR5, have been proposed as potential blocking targets to manage CRS associated with COVID-19 (Figure 3). Finally, complement activation was found to be overactivated in the lungs of patients with COVID-19. Although the results of the randomized trial are not yet published, treatment with anti-C5a monoclonal antibody has shown benefit in two critically ill COVID-19 patients (Gao et al., 2020).
Figure 3. Available Therapeutic Options to Manage COVID-19 Immunopathology: (C) Antagonism of IL-6 signaling pathway and of other cytokine-chemokine-associated targets has been proposed to control COVID-19 Cytokine Release Syndrome (CRS). These include secreted factors like GM-CSF that contribute to the recruitment of inflammatory monocytes and macrophages. (D) Several potential sources of SARS-CoV-2 neutralizing antibodies are currently under investigation, including monoclonal antibodies, polyclonal antibodies, and convalescent plasma from recovered COVID-19 patients (Vabret et al., 2020).

3.2 Therapy with convalescent plasma and neutralizing antibodies (nAbs)

5.2.1 nAbs derived from patients with COVID-19: Patients who have recovered from SARS-CoV-2 infection are a potential source of nAbs (X. Chen et al., 2020; Ju et al., 2020). In an effort to obtain these nAbs, the scientists sorted the RBD-specific memory B cells and cloned their heavy and light variable regions to express recombinant forms of the antibodies (Vabret et al., 2020). A hybridoma producing monoclonal nAb against SARS-CoV-2 offers the potential for therapeutic antibody that can be directly administered to patients to block ongoing infection and potentially even prophylactically (Figure 3).
Table 1. Strategies to Isolate SARS-CoV-2 Neutralizing Antibodies

<table>
<thead>
<tr>
<th>Ab Source</th>
<th>Clone</th>
<th>Target</th>
<th>Type of antibody</th>
<th>Neutralization</th>
<th>Inhibition of ACE2/RBD Binding</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>derived from Covid-19 patients</td>
<td>31B532D4</td>
<td>RBD</td>
<td>human monoclonal</td>
<td>yes</td>
<td>yes</td>
<td>(Chen et al., 2020)</td>
</tr>
<tr>
<td></td>
<td>P2C-2F6P2C-1F11</td>
<td>RBD</td>
<td>human monoclonal</td>
<td>yes</td>
<td>yes</td>
<td>(Ju et al., 2020)</td>
</tr>
<tr>
<td>derived from sars-cov-1 patients or Mers cov-1 animal models</td>
<td>S309</td>
<td>RBD</td>
<td>Human monoclonal</td>
<td>Yes</td>
<td>No</td>
<td>(Pinto et al., 2020)</td>
</tr>
<tr>
<td></td>
<td>R325R302R007</td>
<td>S1</td>
<td>rabbit monoclonal</td>
<td>yes</td>
<td>No</td>
<td>(Sun et al., 2020)</td>
</tr>
<tr>
<td></td>
<td>47D11</td>
<td>S1</td>
<td>recombinant human monoclonal (derived from hybridomas of immunized transgenic H2L2 mice)</td>
<td>yes</td>
<td>No</td>
<td>(C. Wang et al., 2020)</td>
</tr>
<tr>
<td>VHH-72-Fc</td>
<td>S</td>
<td>Fc-fusion derived from camels VHH</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>(Wrapp et al., 2020)</td>
</tr>
</tbody>
</table>

5.2.2. SARS-CoV-1 nAbs also neutralize SARS-CoV-2: the SARS-CoV-1 and SARS-CoV-2 consensus sequences share approximately 80% identity (Tai et al., 2020). Thus, a wide range of SARS-CoV-1 nAbs have been tested for cross-reactivity with SARS-CoV-2, as they could help accelerate the development of potential treatments for COVID-19. In a recent study, antibodies were isolated from the memory B cells of an individual who recovered from an infection with SARS-CoV-1. While 8 of the 25 antibodies isolated could bind to the SARS-CoV-2 S protein, one of them (s309; see Table 1) also neutralizes SARS-CoV-2 (Pinto et al., 2020).

5.2.3 nAbs Derived from Animals: Animal models represent another tool for generating nAbs against SARS-CoV-2 (Table 1). In one study, the authors developed a protocol to synthesize human nanobodies, smaller antibodies that contain only one variable heavy chain (VH) as first described in camels (Wu et al., 2020) (Figure 3). Another antibody isolated from camels immunized with the SARS-CoV-1 and MERS-CoV S proteins and then fused to a human Fc fragment showed neutralization potential against SARS-CoV-2 (VHH-72-Fc) (Wrapp et al., 2020). Mice genetically engineered with humanized antibody genes can also be used to generate therapeutic monoclonal antibodies, as has been successfully tested against Ebola virus (Levine, 2019). Similar studies are now focused on using SARS-CoV-2 or derivatives to generate highly efficient nAb in animal models, which can be directly administered to infected patients, and efforts are already underway with estimates of clinical trials of pooled antibody cocktails. Finally, another approach to the development of nAb consists in fusing the ACE2 protein and the Fc part of the antibodies, since they would bind to RBD and would be potentially reactive with other CoVs (FIG. 6D). Indeed, it has been shown that an ACE2-Fc (Lei et al., 2020) and an RBD-Fc (Y. Li et al., 2020) neutralize both SARS-CoV-1
and SARS-CoV-2 in vitro.

5.2.4 Convalescent plasma therapy:

Although recombinant nAbs can provide effective treatment, they will require a significant investment of time to develop, test, and scale production before they become widely available to patients. A faster strategy is to transfer convalescent plasma (CP) from previously infected individuals who have developed high titer nAbs that target SARS-CoV-2 (Figure 3). Some studies and case reports of CP therapy for COVID-19 evaluated the safety and potential efficacy of CP therapy in patients with severe disease (Duan et al., 2020; Shen et al., 2020; Zhang et al., 2020) (Table 2). These studies were neither controlled nor randomized, but they suggest that treatment with PC is safe and may have a beneficial effect on the clinical course of the disease. The Food and Drug Administration (FDA) in United States has approved the use of this treatment strategy for patients with severe COVID19 in march 2020 (Tanne, 2020). Several clinical trials are currently underway around the world (Belhadi et al., 2020). A study summarized several reports on COVID-19 describing the safety and effectiveness of convalescent plasma therapy and randomized clinical trials registered for convalescent plasma in COVID-19 in several countries such as Canada, Colombia, Italy, France, India and Egypt (Wooding and Bach, 2020).

Table 2. A selected example of significant clinical trials using Convalescent Plasma Therapy in COVID-19 Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Start of CP Therapy</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 severe patients</td>
<td>between 10 and 22 days after hospital</td>
<td>body temperature normalized within 3 fdays in 4 of 5 patients</td>
<td>(Shen et al., 2020)</td>
</tr>
<tr>
<td>(30-70 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 severe patients</td>
<td>median 16.5 days</td>
<td>disappearance of clinical symptoms after 3 days</td>
<td>(Duan et al., 2020)</td>
</tr>
<tr>
<td>(34-78 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 critical patients</td>
<td>at degradation of symptoms,</td>
<td>clinical improvement</td>
<td>(Zhang et al., 2020)</td>
</tr>
<tr>
<td>(31-73 years)</td>
<td>between 11 and 19 days after hospital admission</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Conclusion

COVID-19 is a complex pathology, especially from an immunological point of view. The immune response developed contributes in 80% of patients to the
elimination of SARS-CoV-2 and their cures without developing symptoms or with mild symptoms. However, in other patients (elderly or with comorbidities or with genetic susceptibility) sars-cov-2 induces activation and exaggerated secretion of pro-inflammatory cytokines by macrophages and epithelial cells which generate lung damage and sometimes other target organs that contribute to the severity of COVID symptoms.

The various studies suggest that most patients develop immunity against the virus, although it is still too early to know the duration of this immunity and its effectiveness against reinfection.

The initial studies on convalescent plasma for COVID-19 and previous coronavirus epidemics are promising, however further randomized trials and control remain to be carried out to assess whether this treatment can be effective against covid19.

Current research should make it possible to better understand the immunological alterations, elucidate the mechanisms of pathogenesis and define the biomarkers predictive of severe diseases in order to be able to practice precision medicine by offering a treatment adapted to the phenotype of the disease. This should lead to a better understanding of the pandemics and aid in the search for effective treatment and vaccines.

References


- Weiskopf, D., Schmitz, K.S., Raadsen, M.P., Grifoni, A.,...


