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REVIEW

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Basic immunology may lead to translational therapeutic rationale: SARS-CoV-2 and rheumatic diseases

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Abstract

COVID-19 pandemia is a major concern for patients and healthcare systems. The fear of infection by patients with concomitant rheumatic diseases (either adult or children) and connective tissue diseases is arising worldwide, because of their immunological background and immunological therapies. Analysing the basic biology of single diseases, the data suggest that there is an "immunological umbrella" that seems to protect against the infection, through IFN type 1 and NK cell function. To date, reports from China, United States and Europe did not reveal an higher risk of infection, either for rheumatoid arthritis, juvenile idiopathic arthritis nor for lupus erythematosus. Antimalarials, anti-IL6-Anti-IL6 receptor, anti-IL1, anti-GM-CSF receptor and JAK1/2/3 inhibitors, are under investigation in COVID-dedicated clinical trials to control the inflammation raised by SARS-CoV-2 infection. Initial reports on the occurrence of autoimmune phenomena in the convalescence phase of SARS-CoV-2 infection suggests that the immunological consequences of the infection need to be strictly understood. Reporting of the study conforms to broad EQUATOR guidelines (Simera et al January 2010 issue of EJCI).

KEYWORDS

COVID-19, geriatrics, pathophysiology, pediatrics, rheumatology, rheumatology, SARS-CoV-2

1 | INTRODUCTION

The outbreak of COVID-19 (SARS-CoV-2 infection) leading to a worldwide pandemia has raised fear and anxiety in the whole world populations. Yet even more concern, scare and worry have emerged among patients with concomitant rheumatic diseases, who believe to be at higher risk of developing the threatening acute respiratory distress syndrome that lead some SARS-CoV-2 infected people to death.[1] Meanwhile, while waiting for a robust anti-viral drug, still unknown,[2] and even more for a vaccine, we faced a tremendous challenge in our clinical practice as rheumatologists. In this review, we summarize some of the scientifically proven evidences that will eventually lead to lower the overall concern and fear for the patients with rheumatic disorders as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE). The first evidence is that no reports have been published until now that patients with concomitant rheumatological diseases are at increased risk of hospitalization or access to intensive care units (ICU).[3] The second evidence is that initial data have been provided on the rate of ICU access need in rheumatic patients after SARS-CoV-2 infection in China as well as in Europe.[4] The third evidence is that some drugs used in rheumatological patients (Chloroquine, Hydroxychloroquine

and anti-IL6/IL6-R therapy) have been considered among the possible adjunctive therapeutics in the armamentarium to treat SARS-CoV-2 infected patients and were included in several ongoing clinical trials in several countries worldwide. The final evidence is that children may develop pneumonitis, yet older subjects with comorbidities are at much higher risk in the general population.[5,6] All these data are reassuring.

2 | PATHWAYS OF SARS-COV-2 INFECTION AND INFLAMMATION

Once SARS-CoV-2 virus invades the human host, the first step is to neutralize the agent from replication and spreading. The first receptor that hooks the virus to the membrane of mucosal epithelial cells [nose, trachea, alveolar type 2 (AT-2) cells] is represented by the angiotensin-converting enzyme type 2 (ACE2) receptor which is particularly expressed along with the virus S protein priming protease TMPRSS2, in the nosal goblets and ciliary cells.[7] This interaction leads to the fusion of the virus with the membrane, release of viral ssRNA and binding to pattern recognition receptors (PRR). Among the PRR, three major receptors are involved in viral infections: Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs).[8] Once AT-2 cells are infected, they raise an innate immune response by secreting IFN β, IFN γ, IL6, IL8 and others.[9]

The SARS-CoV ssRNAs virus links TLR7-8 (endosomal receptor are TLR 3,7,8 and 9), which are expressed significantly in airway epithelial cells (AEC),[10] and in dendritic cell (DCs), and signal downstream through adaptor proteins Myd88, which leads to the activation of the transcription factor nuclear factor-κB (NF-κB) and interferon regulatory factor 7 (IRF7) with the production of type I interferons (IFN-α/β) and a series of pro-inflammatory cytokines among which also granulocyte-monocyte colony-stimulating factor (GM-CSF) and IL17 and others.[11-13] Thus, IFN-α/β and IL6 (and other cytokines) are synthesized which enable, within a balanced host anti-viral immune response, the clearance of the virus. This can occur, at least in animal models, if there is an IFN-α/β response and when a low inflammatory-monocyte macrophages response occurs.[13] Conversely, if the viral challenge, instead, inhibits type I IFNs function, by many strategies (ie inhibition of IFN synthesis, interference of IFN receptor signalling),[14] the synthesis of pro-inflammatory cytokines aberrantly increases promoting the recruitment of macrophages and neutrophils into the alveoli, inducing a local hyper-immune response[15,16] that can progress towards an acute respiratory distress syndrome (ARDS) and in some cases to death. At this phase of the diseases, a dysregulated type I IFN response and a macrophage/monocyte inflammatory hyper-response may cause lethal pneumonia.[16-18]

Highlights

1. The outbreak of SARS-Cov-2 infection affected mostly the weaker persons in the world (ie elderly).
2. The biology of RA, JIA and SLE seems to create a protective " umbrella" for SARS-CoV-2 infected patients (ie IFN type 1 and NK cells)
3. Patients suffering from RA, JIA or SLE did not emerge among the categories at increased risk and the therapeutics used in patients were not predisposing factors.
4. The COVID-19 pathology appears to have three clinical phases, with different biology, likely to be treated differently. The final phase may end up with NETosis-microangiopathy.
5. The occurrence of microvascular endothelial damage and of antiphospholipid antibodies in some COVID-19 patients raises concern over the long term of possible new chronic inflammatory-autoimmune diseases.
6. Patients, with concomitant rheumatic diseases, should continue all their therapies, unless differently suggested by their caring physician, without anxiety, saving as much as possible glucocorticosteroids.

Therefore, this means that there might be at least three possible sequential clinical phases of the SARS-CoV-2 infection in human: a normal inflammatory immune response mainly localized inside the infected alveolar epithelial cells type 2 (AT-2) (viral replication), with no or few symptoms (first phase). A Bronchial-alveolar inflammatory immune response with a low inflammatory-monocyte macrophages-polymophonuclear response (viral replication with acute inflammatory response) (second phase) and a hyper-inflammatory host immune response (with or without the virus) with hyper IFN type I synthesis and cytokine storm (third phase) (Figure 1).

3 | INNATE IMMUNE RESPONSE CONSEQUENCES ACCORDING TO AGE AND GENDER IN HEALTHY SUBJECTS

It has been suggested that SARS-CoV-2 virus may enter AT-2 cells through the ACE2 receptor on the membrane of AT-2 cells and employs the serine protease TMPRSS2 for priming the S protein of the virus leading to the subsequent

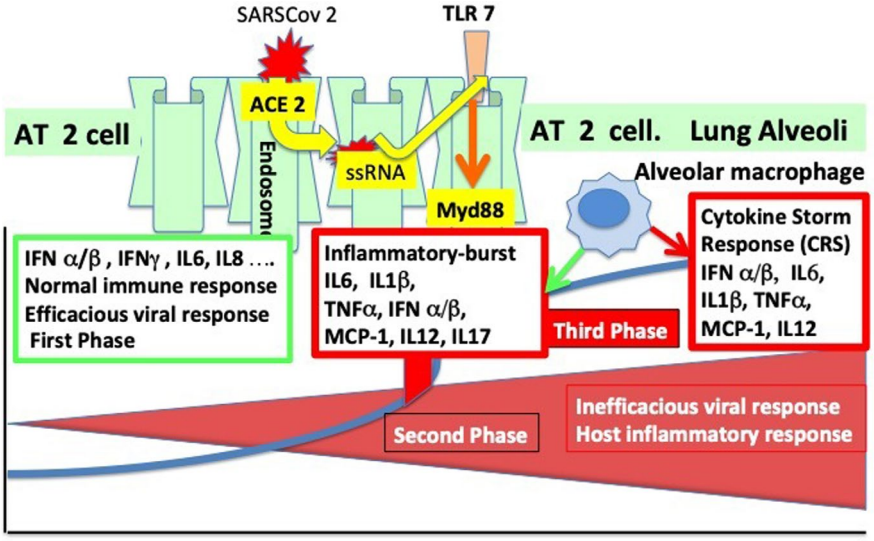

FIGURE 1 AT2 cells innate immune response against SARS-CoV-2 and clinical disease course in human. SARS-CoV-2 enters into the cell and leads to the synthesis of IFNα/β, IFNγ, IL6 and IL8 and their release; the viral ssRNA binds TLR7/8 and activates Myd88. This replication phase is the target of the anti-viral therapy combined with targeted anti-inflammatory therapy. The second phase is the inflammatory phase in which the innate immune response elicited by alveolar type 2 cells, and by the activation of TLR7, binding ssRNA of SARS-CoV2 leads to the recruitment of alveolar macrophages producing high levels of cytokines-chemokines. The third phase is characterized by the biological scenario of the cytokine releasing syndrome (CRS) in which the virus might even be absent. In this contest, two phenotypes eventually might evolve to macrophage activation (MAS)-like or haemophagocytic lympho-histocytosis (HLH)-like syndrome and different approaches should be devised

endosomal fusion inside the cell.[19] A reduction of ACE2 membrane expression, which is shut-down by COVID-19, contributing to ARDS development (along with IL6), and might be a target in the infection-induced ARDS[20] suggesting a crucial role of the viral load in the induction of clinical complication in the follow-up.

The innate immune cells [mostly polymorphonuclear (PMN) cells, innate lymphoid cells (ILC) especially ILC2, natural killer (NK) cells and others] are recruited by cytokines and chemokines released during the early response by professional antigen-presenting cells and further amplify the immune response, using TLRs and promoting the cytokine burst. Among those, innate NK cells (in their different subtypes) are of crucial physiological importance because they are enriched of TLR7 (and other TLR) and produce either IFN type I (acting mainly on STAT 1 and 2 trough JAK1-Tyk 2) as well as IFN-γ type II. In addition to NK cells, ILC-2 cells are important to keep lung integrity playing a key role in host defence against viral infection since the transfer of ILC-2 derived from young mice in the lung of elderly mice enhances mice resistance to infection.[21]

To understand why SARS-CoV-2 infection affects mainly older patients in whom it causes a more severe illness, we must recap the function of the innate immune system according to age and sex. As we stated before, AECs, DCs and NKs play a fundamental role in the early phase of defence, as usually happens during Influenza, also an ssRNA virus.[22,23] Moreover, it must be pointed out that TLR 7 gene is encoded by X chromosome, and women can display much more molecules than men.[24] Since TLR7 is of fundamental importance in response to self-ssRNAS and critical in the various steps of defence against viral infection through the production of IFN type I, the lower response in males might be crucial in favouring more infections in the male gender. Therefore, the host is key in halting or favouring the progression of the infection, being the baseline immune competence critical. When analysing the physiology of the innate immune system, NK cells are higher in infancy and decrease progressively with aging, as well as neutrophils, and lymphocyte number and function also decline with age,[25] with $CD8^{pos}$ T cells function decreasing more with aging.[21] In addition, TNFα and IL6 levels increase with age and may contribute to increased inflammation in the lungs.

These data may represent some of the biological reasons why elderly people are more severely affected by SARS-CoV-2 infection and why morbidity and mortality in children, young adults and especially women, are not higher.

4 | ADAPTIVE IMMUNE RESPONSE

Most of the studies published so far addressed the characteristics of the acute severe phases of the SARS-CoV-2 disease. In fact, preliminary data demonstrated a profound alteration of the T innate immune response, affecting the three major players (mucosal associated invariant T-MAIT, γδT and invariant natural killer T-iNKT cells),

which produce high amounts of IFNγ and IL-17A. A recent study, considering SARS-CoV-2 infected patients hospitalized in ICU, reported that MAIT and iNKT cells were profoundly depleted (6-folds and 7-folds, respectively) in peripheral blood, but dramatically enriched in endotracheal aspirates,[26] demonstrating that there is a compartmentalization in the lung of these cells, where there is a strong recruitment of innate immunity cells. These results are supported by the data emerged from a German study addressing the possible involvement of the adaptive T-cell immune response in the SARS-CoV-2 infection. In particular, patients with critical clinical forms of COVID-19 demonstrated a strong response of SARS-CoV-2-reactive T cells ($CD4^{pos}CD154^{pos}$) producing Th1 associated inflammatory cytokines and a correlation with IgG antibody titres against SARS-CoV-2.[26] Of interest in the same study, a strong gradual reduction in the frequencies of transitional and marginal zone $CD19^{pos}$ cells in patients with severe or critical symptoms was seen without changes in switched $CD19^{pos}IgD^{neg}$ plasmablasts levels. In a study from United States, considering patients with mild and severe COVID-19 disease, Sanz and colleagues assessed the B-cell compartment in SARS-CoV-2 infected patients finding an enrichment of double negative (DN2- IgD-CD27-) B cells, characterized by high production of antibodies, high expression of CD11c and T-bet and TLR7.[27] Interestingly, the DN2 B cells showed a striking hyper-plasmablast differentiation response to TLR7 agonists whose hyper-responsiveness is crucial in the promotion of pathology [28] mediated by IL21,[28] IL6 and IFNα.[29]

5 | CONSEQUENCES IN RHEUMATIC PATIENTS RECEIVING IMMUNOSUPPRESSIVE TREATMENTS

Patients with rheumatological diseases have an immunological hyper-activated biological background, linked mainly to their concomitant autoimmune disease, that do not strongly predispose to viral infections. In particular, SLE and RA patients show an enrichment of mononuclear cells with an IFN type 1 signature that correlates with specific autoantibodies.[30-33]

In systemic JIA, the stimulation of peripheral blood with multiple ligands revealed a shift towards increased pro-inflammatory responses elicited by IL-1–β inducing TLR4 and TLR8 ligands and a concomitant decrease in TLR7 and IFN responses.[34,35] Moreover, whether the vaccinations received by kids during the first years of life and during childhood contribute to a better response against the infections is still a matter of intense research.[36] However, these data along with the NK cells activity described above support the idea that the patients overall (with exceptions) are protected by a cellular (NK-driven) and molecular (IFN type 1-driven) umbrella.

5.1 | Autoimmune chronic inflammatory diseases and therapies

Many patients with SLE or RA receive antimalarials [as hydroxychloroquine or chloroquine], and there are several report that show that antimalarials as hydroxychloroquine sulphate is a drug which can inhibit TLR7/9 signalling.[37] Moreover, chloroquine was shown to be effective in controlling influenza A H5N1 in animal models [38] but not in humans. This is thought to occur by raising the lysosomal pH, required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV-2. In additional, Chloroquine might function at both entry, and at intracellular stages of the SARS-CoV-2 infection and, due to its favourable kinetics, is distributed in the whole body, including lung, after oral administration.[39] To date, more than 100 trials are ongoing testing hydroxychloroquine, although there are no randomized trials suggesting that it is worth treating SARS-CoV-2 infected patients just for prophylactice nor therapeutic purposes (Table 1). The report of the possible development of antiphospholipd antibodies (APL) and the following thrombotic consequences suggest that a tight rheumatological surveillance is tremendously needed and the post-infection immunologic consequences should be deeply assessed.[40,41] In addition, the demonstration of microvascular thrombosis and evidence of aberrant NET formation [42] strongly support the discrepancy observed between hypoxia (even very severe) and lung CT damage in several patients that suggested an alveolar-vessel barrier which is damaged on the endothelial side,[43] suggesting the development of thromboinflammation [42] phenomena which may be associated with a negative course of lung function and with lung failure.

Furthermore, to better understand how to control pharmacologically the inflammation cascade characterizing the second and third phases of the disease, multiple clinical trials have been designed with at least 8 drugs used in the clinics, in different countries, among which also Leflunomide (Clinicaltrials.gov; Table 1).

5.2 | Targeting single innate immunity molecules

Targeting IL6 seems to be an effective therapeutic options able to repress the acute inflammation and the cytokine storm occurring inside the lung of patients in the latest phase of SARS-Cov-2 infection, translated from the therapeutic approach to treat the cytokine release storm (CRS) syndrome which may develop after Car-T therapy in patients with acute leukaemias.[44]

TABLE 1 Molecules registered in Clinicaltrials.gov to treat patients with SARS-CoV-2 infection

Molecular target	Drug	No of registered trials[a]
Anti-IL6-R	Tocilizumab	37
Anti-IL6-R	Sarilumab	14
Anti-IL6	Siltuximab	3
Anti-IL6	Clazakizumab	4
Anti-IL1-R	Anakinra	18
Anti-GM-CSF-R	Mavrilimumab	2
Anti-GM-CSF	Gimsilumab	1
Anti-IFNγ	Emapalumab	1
JAK1-2	Baricitinib	15
JAK1-3	Tofacitinib	4
JAK1-2	Ruxolitinib	18
	Leflunomide	1
	Hydroxychloroquine	>100

Note: GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IFN, Interferon; JAK, janus kinase.

[a]Clinicaltrials.gov.

The efficacy of controlling IL6 with anti-IL6-receptor antibodies (ie Tocilizumab or Sarilumab) or directed against IL6 (Clazakizumab, Siltuximab) suggests that the balance between the anti-inflammatory and the excessive pro-inflammatory effects can be crucial at the lung level.[44] In addition, due to the importance in the innate immune response of molecules as IL1, GM-CSF and IFN-γ, clinical studies testing anti-IL1 (using IL1 Receptor antagonist-IL1Ra—Anakinra) as well as anti-GM-CSF (granulocyte-macrophages colony-stimulating factor-receptor—Mavrilumumab) or granulocyte-macrophage colony-stimulating factor (Gimsilumab) and anti-IFN-γ (interferon gamma-Emapalumab) are currently ongoing (Table 1). On the other hand, TNF inhibitors (TNF-I) might increase the risk of possible viral infections [45] since TNF α impairs viral clearance by blocking the host autophagy response, which is usually used by host cells to degrade unnecessary or dysfunctional cellular components, but is critical to eliminate intracellular viral particles.[46] Despite limited data were provided so far on the risk rate of SARS-CoV-2 in rheumatic patients treated with these drugs, no data are available on whether patients on TNF-I are at higher absolute risk of infection and the maintenance a low level of inflammation of the concomitant rheumatological disease by continuing TNF-I appears to be the safest strategy.

5.3 | Targeting multiple cytokines (JAK inhibitors)

Since the cytokine burst involves several cytokines, the inhibition of JAK1, JAK2 and/or JAK3 may be successful strategy to repress the whole storm. Moreover, it is a general concern that therapy with JAK inhibitors could be detrimental because of their possible effect on the IFN-type 1 response, and it is known that JAK inhibitors, mainly JAK-1-2 inhibitor, reduces Type-I and Type-II IFN-induced phosphorylation (pSTAT1) in vitro. In particular, Baricitinib showed a high affinity for AAK1, one of the kinases along with GAK, belonging to the Numb family kinases (NAK), mediating the clathrin endocytosis which is a fundamental step for the virus entry inside the epithelial cells of the airway tract. Based on these preliminary data, 15 clinical trials are registered with Baricitinib (at a daily dose of 4 mg/day and 2 mg/day, respectively) to treat SARS-CoV-2 infection. Among the various JAK inhibitors (ruxolitinib, fedratinib, tofacitinib), Baricitinib showed the highest inhibition of AAK1 in vitro. AP2-associated protein kinase 1 (AAK1) is a key regulator of viral endocytosis and disruption of AAK1 signal might, in turn, interrupts the passage of the virus into the cells and also the intracellular assembly of virus particles.[47,48] If this is the case in vivo, patients under JAK inhibitor should be more prone to avoid the infection. No data are available on this issue, and it is urgently needed to collect data to support the rationale. In fact in case of SARS-CoV-2 exposure, the IFN response is necessary for an efficient anti-viral response and a temporary withdrawal of the drug should be the safer biological approach from the immunological point of view. However, in the third phase of the disease, the use of JAK 1/2 inhibitor, once the virus already has evaded the IFN control,[49] could be an effective therapeutic to shutdown the cytokine storm. Therefore, controlled studies of possible sequential therapies following the dynamics of the disease course are strongly needed.

5.4 | Targeting the adaptive immune response

Targeting the adaptive immune response, which is so important for the development of neutralizing antibodies, appears valueless, and no clinical trials, regarding Abatacept or anti-CD20, are registered in clinical.trials.gov. This is clearly understandable since the herd immunity should be the final goal to achieve the highest rate of population protection.

As stated in a recent paper by Winthrop and colleagues,[45] there are no data that can really highlight whether the risk of infections in rheumatic patients taking their drugs (either in RA, SLE, JIA) is increased or not. The data available do not show an increased hospitalization, nor an increased access to ICUs.[50] We certainly needed clear-cut information from large databases as the one developed by the European League Against Rheumatism (EULAR).[51] With these information at hand, we can state that none of the therapies should be

withdrawn, unless necessary, due to their helpful action in the inflammation control. However, a caveat regards the steroids therapy, often used in rheumatological patients, that has an intrinsic risk of predisposing to infections,[52] as recently endorsed by the American Thoracic Society [53] by which, whenever possible, very low doses or no steroids should be the best way to keep safe. Despite this caveat, there are some clinical settings in which steroids are adopted, as in advanced ARDS cases or as in the recent case report of a SARS-CoV-2-related myopericarditis treated with a mixture of drugs including glucocorticosteroids.[53,54] In this contest, a prompt telemedicine consultation with the rheumatologist may help to solve anxiety and doubts in patients already under treatments.[55] The key point is that the patients with RA, JIA or SLE should keep their therapies, as suggested by NICE recommendations.[56] Moreover, all the immunological consequences of SARS-Cov-2 infection will need to be understood and fully defined in the long-term convalescence phase.

6 | CONCLUSION

Few reports have been published on the risk of hospitalization or access to ICU of rheumatic patients exposed to SARS-CoV-2 infection. Multinational clinical trials are currently testing the effect of different anti-rheumatic drugs in COVID-19. Moreover, older subjects with multiple comorbidities are at higher risk of severe clinical sequelae after infection in the general population, while children rarely develop severe infection leading to ICU access need as recently suggested investigating a wide Italian cohort of liver transplanted children, of whom 100 with autoimmune diseases, and only 3 showed positive RT-PCR at nasopharyngeal swabs with nobody developing pneumonitis.[57,58]

During the pandemic, multiple drugs currently used to treat rheumatological conditions have been proved to have potential efficacy in SARS-CoV-2 infected individuals and several explorative clinical trials are ongoing to test their efficacy and biological effect. However, future studies will be crucial to assess their efficacy to treat individual phases across the course of the disease.

CONFLICTS OF INTEREST

None of the authors has any potential financial conflict of interest related to this manuscript.

AUTHOR CONTRIBUTION

EG: Criterion 1: a) substantial contribution to study conception and design; b) substantial contribution to acquisition of data; c) substantial contribution to analysis and interpretation of data—Criterion2: Drafted the paper for its intellectual content—Criterion 3: Finally approved the version of the submitted article. ESF: Criterion 1: a) substantial contribution to study conception and design; b) substantial contribution to acquisition of data;—Criterion2: Drafted the paper for its intellectual content—Criterion 3: Finally approved the version of the submitted article. SA: Criterion 1: b) substantial contribution to acquisition of data; c) substantial contribution to analysis and interpretation of data—Criterion2: Drafted the paper for its intellectual content—Criterion 3: Finally approved the version of the submitted article. BT: Criterion 1: b) substantial contribution to acquisition of data; c) substantial contribution to analysis and interpretation of data—Criterion2: Drafted the paper for its intellectual content—Criterion 3: Finally approved the version of the submitted article. GF: Criterion 1: a) substantial contribution to study conception and design; c) substantial contribution to analysis and interpretation of data;—Criterion 2: Drafted the paper for its intellectual content—Criterion 3: Finally approved the version of the submitted article.

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