INTRODUCTION

The outbreak of COVID-19 (SARS-CoV-2 infection) leading to a worldwide pandemic 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. Meanwhile, while waiting for a robust anti-viral drug, still unknown, 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 rheumatic diseases are at increased risk of hospitalization or access to intensive care units (ICU). Meanwhile, while waiting for a robust anti-viral drug, still unknown, 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 rheumatic diseases are at increased risk of hospitalization or access to intensive care units (ICU). The second evidence is that initial data has been provided on the rate of ICU access need in rheumatic patients after SARS-CoV-2 infection in China as well as in Europe. The third evidence is that some drugs used in rheumatological patients (Chloroquine, Hydroxychloroquine, 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).
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. 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 nasal goblets and ciliary cells. 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). Once AT-2 cells are infected, they raise an innate immune response by secreting IFN β, IFN γ, IL6, IL8 and others.

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), 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. 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. Conversely, if the viral challenge, instead, inhibits type I IFNs function, by many strategies (ie inhibition of IFN synthesis, interference of IFN receptor signalling), the synthesis of pro-inflammatory cytokines aberrantly increases promoting the recruitment of macrophages and neutrophils into the alveoli, inducing a local hyper-immune response 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.

### 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 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
endosomal fusion inside the cell. 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 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.

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. Moreover, it must be pointed out that TLR 7 gene is encoded by X chromosome, and women can display more molecules than men. 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, with CD8Pos T cells function decreasing more with aging. 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-iNK T cells), 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.
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, 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 (CD4posCD154pos) producing Th1 associated inflammatory cytokines and a correlation with IgG antibody titres against SARS-CoV-2. Of interest in the same study, a strong gradual reduction in the frequencies of transitional and marginal zone CD19pos cells in patients with severe or critical symptoms was seen without changes in switched CD19posIgDneg 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. 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 mediated by IL21, IL6 and IFNα.

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.

In systemic JIA, the stimulation of peripheral blood with multiple ligands revealed a shift towards increased pro-inflammatory responses elicited by IL-1β inducing TLR4 and TLR8 ligands and a concomitant decrease in TLR7 and IFN responses. 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. 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. Moreover, chloroquine was shown to be effective in controlling influenza A H5N1 in animal models 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 addition, 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. 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 prophylactic nor therapeutic purposes (Table 1). The report of the possible development of antiphospholipid 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. In addition, the demonstration of microvascular thrombosis and evidence of aberrant NET formation 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, suggesting the development of thromboinflammation 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.
The efficacy of controlling IL6 with anti-IL6-receptor antibodies (i.e., 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. 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-macrophage colony-stimulating factor—Mavrilimumab) 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 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. 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 of a low level of inflammation of the concomitant rheumatological disease by continuing TNF-I appears to be the safest strategy.

### 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 I 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.

### 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 clinicaltrials.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, 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. We certainly needed clear-cut information from large databases as the one developed by the European League Against Rheumatism (EULAR). With these information at hand, we can state that none of the therapies should be

### Table 1

| Molecular target | Drug                        | No of registered trials |
|-----------------|-----------------------------|-------------------------|
| 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.

*Clinicaltrials.gov.
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,\textsuperscript{52} as recently endorsed by the American Thoracic Society \textsuperscript{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 myocarditis treated with a mixture of drugs including glucocorticosteroids.\textsuperscript{53,54} In this contest, a prompt telemedicine consultation with the rheumatologist may help to solve anxiety and doubts in patients already under treatments.\textsuperscript{55} The key point is that the patients with RA, JIA or SLE should keep their therapies, as suggested by NICE recommendations.\textsuperscript{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.\textsuperscript{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.

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REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. \textit{Lancet}. 2020;395:1054-1062.
2. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. \textit{N Engl J Med}. 2020;382(24):2327-2336.
3. Guan W-J, Ni Z-Y, Hu YU, et al. Medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. \textit{N Engl J Med}. 2020;382(18):1708-1720.
4. Sinha IP, Harwood R, Semple MG, et al. COVID-19 infection in children. \textit{Lancet Respir Med}. 2020;8:446-447.
5. Lescure F-X, Boudama L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. \textit{Lancet Infect Dis}. 2020;20(6):697-706.
6. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. \textit{Lancet Infect Dis}. 2020;20(6):689-696.
7. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. \textit{Nat. Med}. 2020;26:681-687.
8. Koyama S, Ishii KJ, Coban C, Akira S. Innate immune response to viral infection. \textit{Cytokine}. 2008;43:336-341.
9. Qian Z, Travanty EA, Oko L, et al. Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome–Coronavirus. \textit{Am J Respir Cell Mol Biol}. 2013;48:742-748.
10. Ioannidis I, Ye F, McNally B, Willette M, Flaño E. Toll-Like receptor expression and induction of type I and type III Interferons in primary airway epithelial cells. \textit{J Virolology}. 2013;87:3261-3270.
11. Totura AL, Whitmore A, Agnihotthram S, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. \textit{MBio}. 2015;6:e00638-e715.
12. Channappanavar R, Fehr A, Vijay R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe. 2016;19:181-193.

13. Ferraccioli ES, Grems E, Ferraccioli G. Children’s (and auto-immune patients) morbidity (and mortality) from Covid-19 is similar to the general population: immunologic rationale. Arthritis Rheumatol. 2020;https://doi.org/10.1002/art.41399.

14. Weber F, Kochs G, Haller O. Inverse interference: how viruses fight the interferon system. Viral Immunol. 2004;17:498-515.

15. Ritter M, Mennerich D, Weith A, Seither P. Characterization of Toll-like receptors in primary lung epithelial cells: strong impact of the TLR3 ligand poly(I:C) on the regulation of Toll-like receptors, adaptor proteins and inflammatory response. J Inflamm (Lond). 2005;2:16.

16. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39:529-539.

17. Lemaire I, Yang H, Lafont V, Dornand J, Coomes T, Cantin MF. Differential effect of macrophage-and genulocyte-macrophage colony stimulating factors on cytokine gene expression during rat alveolar macrophage differentiation into multinucleated giant cell (MGC): role for IL6 in type 2 MGC formation. J Immunol. 1996;157:5118-5125.

18. Cifaldi L, Prencipe G, Caiello I, et al. Inhibition of natural killer cell cytotoxicity by IL6. Implications for the pathogenesis of macrophage activation syndrome. Arthritis Rheumatol. 2015;67:3037-3046.

19. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven Protease Inhibitor. Cell. 2020;181(2):271-280.e8.

20. Khan A, Benthin C, Zeno B, et al. A pilot clinical trial of recombinant human angiotensin converting enzyme 2 in acute respiratory distress syndrome. Crit Care. 2017;21:234.

21. Mindt BC, Fritz JH, Duerr CU. Group 2 innate lymphoid cells in pulmonary immunity and tissue homeostasis. Frontiers Immunol. 2018;9:840.

22. Stegemann-Koniszewski S, Behrens S, Boehme JD, et al. Respiratory Influenza A virus infection triggers local and systemic natural killer cell activation via toll-like receptor 7. Frontiers Immunol. 2018;9:245.

23. Hart OM, Athie-Morales V, O’Connor GM, Gardiner CM. TLR7/8-mediated activation of human NK cells results in accessory cell-dependent IFN-γ production. J Immunol. 2005;175:1636-1642.

24. Souyris M, Cenac C, Azar P, et al. TLR7 escapes X chromosome inactivation in immune cells. Sci. Immunol. 2018;3:eaa8855.

25. VALIATHAN R, ASHTANA M, ASHTANA D. Effects of ageing on the immune system: infants to elderly. Scand. J. Immunol. 2016;83:255-266.

26. JOUAN Y, GUILLON A, GONZALES L, et al. Functional alteration of innate T cells in critically ill Covid-19 patients. MedRxiv. 2020. https://doi.org/10.1101/2020.05.03.20089300.

27. Woodruff MC, Ramonell RP, Cashman KS, et al. Critically ill SARS-CoV-2 patients display lupus-like hallmarks of extrafollicular B cell activation. MedRxiv. 2020;https://doi.org/10.1101/2020.04.29.20083717.

28. Jenks SA, Cashman KS, Zumaquero E, et al. Distinct effector B cells induced by unregulated toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus. Immunity. 2018;49:725-739.

29. Jego G, Palucka K, Black J-P, Chalouni C, Pascua V, Banchereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity. 2003;19:225-234.

30. de Jong TD, Vosslander S, Mantel E, et al. Physiological evidence for diversification of IFNα- and IFNβ-mediated response programs in different autoimmune diseases. Arthr Res Ther. 2016;18:49.

31. Castroñeda-Delgado JE, Bastían-Hernández Y, Macias-Segura N, et al. Type I Interferon gene response Is increased in early and established Rheumatoid Arthritis and correlates with autoantibody production. Frontiers Immunol. 2017;8:85.

32. Henriques A, Teixeira L, Inés L, et al. NK cells dysfunction in systemic lupus erythematosus: relation to disease activity. Clin Rheumatol. 2013;32:805-813.

33. Fogel LA, Yokoyama WM, French AR. Natural killer cells in human autoimmune disorders. Arthr Res Ther. 2013;15:216.

34. Cepika A-M, Banchereau R, Segura E, et al. A multidimensional blood stimulation assay reveals immune alterations underlying systemic juvenile idiopathic arthritis. J Exp Med. 2017;214:3449-3466.

35. Gattorno M, Chicha L, Gregorio LA, et al. Distinct expression pattern of IFN-α and TNF- α in juvenile idiopathic arthritis synovial tissue. Rheumatology. 2007;46:657-665.

36. Sánchez-Ramón S, Conejero L, Netea MG, Sancho D, Palomares Ø, Subiza JL. Trained Immunity-based vaccines: a new paradigm for the development of broad-spectrum anti-infectious formulations. Front Immunol. 2018;9:2936.

37. Lamberth M, Zheng W, Latz E, et al. Novel small molecule inhibitors of TLR7 and TLR9: Mechanism of action and efficacy in vivo. Mol Pharmacol. 2014;85:429-440.

38. Yan Y, Zou Z, Sun Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Cell Res. 2013;23:300-302.

39. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-271.

40. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with covid-19. N Engl J Med. 2020;382(17):e58.

41. Paglioni A, Varriano V, Tolusso B, et al. Loss of self-tolerance in SARS-COV-2 infection: immunological assessment of a convalescent cohort. Ann Rheum Dis. 2020;79:213.

42. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potent drivers of Covid-19: neutrophil extracellular traps. J Exp Med. 2020;217:e20200652.

43. Brondani G, Apollonio L, Grems E, Ferraccioli G. Pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol. 2020.

44. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. Crit Care Med. 2017;45:e124-e131.

45. Xing Z, Gauldie J, Cox G, et al. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. J Clin Invest. 1998;101:311-320.

46. Winthrop KL. Who needs a corona? Arthritis Rheumatol. 2020;72(6):874-876.

47. Espín-Palazón R, Martínez-López A, Roca FJ, et al. TNFα impairs rhadoviral clearance by inhibiting the host autophagic antiviral response. PLoS Pathog. 2016;12(6):e1005699.
48. Sanchez GAM, Reinhardt A, Ramsey S, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory Interferonopathies. *J Clin Invest*. 2018;128:3041-3052.

49. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20:400-401.

50. Ten G-S. Strategies of interferon evasion by Viruses. *Cell Host Microbe*. 2017;22:176-184.

51. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the seattle region-case series. *N Engl J Med*. 2020;382(21):2012-2022.

52. Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis*. 2020;1-8.

53. Fardet L, Petersen I, Nazareth I. Common infections in patients prescribed systemic glucocorticoids in primary care: a population-based cohort study. *PLoS Medicine*. 2016;13:e1002024.

54. Wilson KC, Chotirmall SH, Bai C, Rello J: COVID-19: Interim guidance on management pending empirical evidence. *Am Thor Soc*. 2020; https://www.thoracic.org/professionals/clinical-resources/disease-related-resources/covid-19-guidance-pdf

55. Inciardi RM, Lupi L, Zacone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020; https://doi.org/10.1001/jamacardio.2020.1096

56. Perniola S, Alivermini S, Varriano V, et al. Telemedicine will not keep us apart in COVID-19 pandemic. *Ann Rheum Dis*. 2020; https://doi.org/10.1136/annrheumdis-2020-218071

57. COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders. NICE guideline [NG167] Published date: 03 April 2020.

58. D’Antiga L. Coronavirus and immunosuppressed patients. The facts during the third epidemic. *Liver Transpl*. 2020;26:832-834.