COVID-19: the new challenge for rheumatologists. One year later

I. Puxeddu[1], F. Ferro[2], E. Bartoloni[3], E. Elefante[2], C. Baldini[2], C.A. Scirè[4], R. Talarico[2], P. Migliorini[1], M. Mosca[2], S. Bombardieri[5]

[1]*Clinical Immunology Unit,*
[2]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;*
[3]*Rheumatology Unit, Department of Medicine, University of Perugia;*
[4]*Rheumatology Unit, Department of Medical Sciences, University of Ferrara;*
[5]*University of Pisa, Italy.*

Ilaria Puxeddu, MD, PhD
Francesco Ferro, MD
Elena Bartoloni, MD
Elena Elefante, MD
Chiara Baldini, MD, PhD
Carlo Alberto Scirè, MD
Rosaria Talarico, MD
Paola Migliorini, MD
Marta Mosca, MD, PhD
Stefano Bombardieri, MD, MaACR

Please address correspondence to:
Ilaria Puxeddu,
Immunologia Clinica,
Dipartimento di Medicina Clinica e Sperimentale,
Università di Pisa,
via Roma 67,
56126 Pisa, Italy.
E-mail: ilaria.puxeddu@unipi.it

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ABSTRACT

At the beginning of COVID-19, we underlined that this pandemic was a new challenge for rheumatologists. On the one hand, it was necessary to clarify the impact of this new viral disease on the natural history of many rheumatic diseases and, on the other hand, to define the beneficial or harmful effects of the synthetic or targeted therapies used for their treatment.

In addition, we have postulated that in view of the common pathogenetic mechanisms involved, the therapeutic armamentarium currently employed in the management of viral or idiopathic systemic autoimmune rheumatic diseases could be useful to control the "cytokine storm" induced by SARS-COV-2.

One year later, in the present review we have analysed the progress of the knowledge on both these aspects and updated the algorithms initially proposed for a rational use of the synthetic and targeted anti-inflammatory and immunomodulatory agents in the management of COVID-19.

Introduction

At the beginning of this pandemic, we had underlined that COVID-19 could be the new challenge for rheumatologists for several reasons (1, 2). Firstly, it appeared immediately evident that this condition was not simply a viral disease and there are now compelling evidences that its systemic manifestations are related to an abnormal inflammation mediated by an immune reaction to SARS-Cov-2 infection. If so, while challenging the effectiveness of a pure anti-viral therapy, it may be hypothesised the effectiveness of a therapeutic armamentarium commonly used to treat systemic autoimmune inflammatory diseases, either idiopathic or virus-induced, such as HBV vasculitis of HCV-associated mixed cryoglobulinaemia. In the past 30 years the identification of more precise pathogenetic mechanisms and adequate biomarkers to monitor these complex diseases have led to the introduction of more effective synthetic or targeted biological therapies. Since, however, often no single drug is able to control the activity of these diseases and prevent irreversible damage, we have learned over the years how important the choice and dosage of the single drug is and their association, timing and duration of the therapy and their optimal withdrawal, in order to maximise their effectiveness and minimise the potential noxious side-effects in the individual patients. Therefore, in view of the potential similarities between COVID-19 and systemic autoimmune inflammatory diseases, in our first two editorials, we tried to translate our experience and familiarity with the practical use of our drugs into a hypothetical optimal model of the management of the different stages of this new disease (1, 2).

At the same time, as rheumatologists, we were worried how this new viral-induced disease could have affected our patients, often already treated with these drugs and with systemic involvement, and how the restrictions imposed by this pandemic on our clinical practice have modified their follow-up in our clinics.

One year after the beginning of COVID-19 in our countries, we will try to briefly review the enormous efforts made by the scientific community in addressing this new challenge for rheumatologists.

Pathogenesis: where we are and what we need to know

An aggressive inflammatory response and dysregulation of the immune system pathways were immediately observed in the severe COVID-19, with-

out precisely defining the mechanisms responsible for these events. In the last few months, the scientific world has clarified several aspects that regulate the tight interaction between SARS-CoV-2 and host immune system, adding a piece to the complex puzzle of the pathogenesis of COVID-19 (3, 4). To know the correct functioning of the immune system and understanding at which level the virus interferes with it are fundamental to designate targeted therapeutic strategies.

The components of the innate immune system act as first responders for the detection and clearance of viral infections, via direct phagocytosis and cytolysis of infected cells. Innate immune cells secrete pro-inflammatory cytokines that inhibit viral replication, stimulate the adaptive immune response, and recruit other immune cells to the site of infection (5). By releasing enzymes and toxic proteins, neutrophils are able to destroy pathogens and infected cells, Natural killer (NK) cells kill virally infected cells via degranulation, receptor-mediated apoptosis, and antibody-dependent cell-mediated cytotoxicity, and activated dendritic cells (DCs) present pathogen-derived antigens to naive helper T cells to initiate the adaptive immune response. Although in most cases of SARS-CoV-2 infection these processes allow the viral clearance, in some cases an overactive innate immune response can contribute to the pathogenesis and severity of COVID-19, involving the release of pro-inflammatory cytokines (IL-6, IL-17A, INF-γ, TNF, GM-CSF, IL-2, IL-7) and chemokines (CXCL1, CXCL2, CXCL6), with the consequent recruitment of macrophages, monocytes and lymphocytes into the tissue (6-8). Activation of macrophages/monocytes and cell pyroptosis seem to actively contribute to the development of the cytokine storm (5), which is responsible for the spread of lung inflammation and progression to acute respiratory distress syndrome (ARDS) in severe COVID-19. It also appears that through the ability of multiple viral structural proteins, SARS-CoV-2 antagonises the interferon responses which are essential for a correct viral clearance (5).

In this complex scenario, neutrophils play a fundamental role. The persistence of these cells in the blood stream and the increase of the neutrophil-lymphocyte ratio predict poor outcomes of COVID-19 (9). This seems to be mainly due to their reduced ability to counteract the virus and their ability to form neutrophil extracellular traps (NETs) (10), contributing to the development of inflammatory processes, hyper-coagulation and thrombosis in arteries and veins (11, 12). In parallel, NK cells, responsible for killing infected cells, by over-expressing their inhibitory receptor NKG2A seem to lose their relevant functions and their ability to produce CD107a, IFN-γ, IL-2, granzyme B, and TNF-α during SARS-CoV-2 infection (13, 14).

As observed in the innate immune system, SARS-CoV-2 is capable of interfering with the correct functioning of some pathways of the adaptive immune response. If the cellular components of the innate immune system are not able to exert an effective clearance of the virus, the drastic reduction of lymphocytes, particularly $CD4^+$, $CD8^+$ T cells and memory cells, leads to a dysregulation of the adaptive immune response, essential in the final viral clearance, as well as in the prevention of re-infection. Coordinated SARS-CoV-2-specific adaptive immune responses were associated with milder but not with the severe disease, suggesting protective roles for both $CD4^+$ and $CD8^+$ T cells in COVID-19 (15). The dynamic changes of lymphocyte subsets and an increase of a certain cytokine profile seem to be crucial for the development of severe COVID-19. The virus has the power to reduce both T and B cell activities and cause a delay in T cell pathways during the first days of infection, which is not always restored in the later stages of the disease.

Until few months ago, there was no evidence to support the hypothesis of a link between autoimmunity and COVID-19. Only some recent reports support a close relationship between SARS-CoV2 infection, hyperactivation of the immune system and the development of an autoimmune response (16). In fact, some SARS-CoV-2 infected patients may have symptoms or laboratory findings that overlap with those commonly described in autoimmune diseases, including cutaneous rashes and vasculitis, autoimmune cytopenia, antiphospolipid syndrome (APS), central or peripheral neuropathy, myositis and myocarditis (16). These seem to occur in genetically predisposed individuals with particular HLA genetic polymorphisms (17-19), through aberrant activation of immunological pathways, including mimicry between viral and self-epitopes, breakdown of tolerance or super-antigen presentation. The hypothesis that SARS-CoV-2 can act as a trigger for autoimmunity has found confirmation in some cases of ischaemia and cerebral infarcts in COVID-19 patients associated with positivity of anti-cardiolipin and anti-β2-glycoproteins (IgA and IgG), suggesting an APS (20). The presence of antibodies such as lupus anticoagulant, anti-52 kDa and anti-60 kDa Ro-SSA, ANA, ACPA, ANCA, ASCA IgA, anti-MAD5 found in some cases of COVID-19 has not yet found a precise location in terms of pathogenicity (21-25). Therefore, whether an autoimmune response following SARS-CoV-2 infection can spontaneously recover or rather lead to a full-blown autoimmune disease will need to be thoroughly investigated. Furthermore, the need to identify the presence of auto-antibodies produced following SARS-CoV-2 infection is not only linked to the possibility of developing autoimmune disorders, but also to identify the presence of auto-antibodies directed to soluble mediators of the immune system that are required for the correct clearance of the virus. In fact, the recent finding of neutralising IgG auto-antibodies against type I IFNs in patients with life-threatening COVID-19 could partly explain the reduced ability of type I IFNs to block SARS-CoV-2 infection (26). Although many aspects of the pathogenesis of COVID-19 have been clarified in these months, there are still some aspects of interaction between the virus and the host immune system that need to be elucidated. Morphological and functional evaluations of immune cells in the follow-up of patients with previous disease may help to better under-

stand the long-term effects of the virus on the immune system.

Corticosteroids in COVID-19: where we are?

As hypothesised in our previous reports (1, 2), the "general paradigm" that steroids may effectively block the post-infectious inflammatory response has nowadays appeared to be true also in severely ill COVID-19 patients. At the beginning of the outbreak, several issues were raised against the use of corticosteroids in COVID-19 patients as they might have hampered the virus clearance and fostered infectious complications. However, the biological rational for the use of corticosteroids in this disease has been demonstrated in autopsy studies showing the presence of lymphocyte alveolitis, organising pneumonia and endothelial cell activation which are all commonly detected also in systemic autoimmune diseases (27). Indeed, the Recovery Collaborative Group study (28) and the results of the meta-analysis by Sterne *et al*. (29) have highlighted the effectiveness of dexamethasone at a dose of 6 mg daily for 10 days in reducing the 28-day mortality of hospitalised patients with severe COVID-19 who were receiving either invasive mechanical ventilation or oxygen alone at randomisation, thus modifying the current therapeutic approach. The current protocols assume that a fixed dose of dexamethasone for a fixed time should be adopted in severely ill COVID-19 patients. If on the one hand the clinical useful of dexamethasone in the treatment of patient with COVID-19 has already been established, it may cast doubt on the effectiveness and safety of the use of 6 mg of a long-acting corticosteroid for 10 days. In fact, it may be possible that this therapeutical approach is inadequate to control the disease in some of the patients with hyperinflammatory state, or, on the other hand, the prolonged use of long-acting corticosteroids may favour both metabolic complication and opportunistic infections. These are some of the reasons why dexamethasone is generally scarcely used in the management of the most severe systemic inflammatory autoimmune diseases and particularly in combination with other immunomodulating agents (30).

There is, therefore, an urgent need to optimise the dosing and the safety of the use of corticosteroids in COVID-19. From this perspective, the available literature and the experience gained in rheumatology with systemic autoimmune diseases indicate three major points to consider. The first is the timing of glucocorticoid prescription. The lesson learned with HCV-associated cryoglobulinaemic vasculitis (HCV-CV) tells us that antiviral agents can assure sustained virologic response in the early stages of the disease; nonetheless, these drugs may fail to suppress the immune-mediated processes once they have been triggered (31). By contrast, despite the potential risk of exacerbation of the infection, corticosteroids and immunosuppressive drugs are generally considered as the first-line intervention in CV, especially if renal involvement is severe (32). From this perspective, it is likely that in the early phase of the SARS-CoV2 infection the use of corticosteroids might be ineffective or even harmful. Indeed, in the Recovery trial, the incidence of death was lower in the dexamethasone group than that in the usual care group of patients receiving invasive mechanical ventilation and those receiving oxygen without invasive mechanical ventilation, but not among those without respiratory support at randomisation. However, in patients undergoing a post-infectious inflammatory response, glucocorticoids may play a pivotal role in limiting the cytokine storm and controlling the inflammatory cascade, similarly to what happens when they are used to induce the remission of systemic autoimmune diseases.

The second point to consider is the type of glucocorticoids to be utilised. Dexamethasone is a synthetic long-acting corticosteroid characterised by a longer duration of action (36–72 h) than prednisone/prednisolone which are intermediate-acting (12–36 hours) (33). Data on efficacy of prednisone and methylprednisolone have remained more limited than those for dexamethasone, even if the available literature seems to indicate that they can be equally effective (34). Noteworthy, in rheumatology, prednisone and methylprednisolone (particularly as a single dose, in the morning) represent the first choice to induce and maintain remission of chronic autoimmune disorders due to their efficacy-safety profile even in the long term (35, 36). To avoid side effects such as infective or metabolic complications or inhibition of the hypothalamic-pituitary adrenocortical (HPA) axis activity, dexamethasone has generally been used in COVID-19 for short periods (37).

The alternative use of prednisone and methylprednisolone may allow more flexible tapering, thus limiting the risk of infections and improving the overall prognosis of the patients, particularly when corticosteroid therapy is associated with other synthetic or targeted anti-inflammatory or immunosuppressive therapies.

Last but not least, considering the use of prednisone and methylprednisolone in rheumatology, a third point that remains uncertain is the possible role of intravenous methylprednisolone pulses (*e.g*. 3 infusions of 10–15 mg/kg) in the most severe patients, given that the very high doses may achieve additional therapeutic benefits through non-genomic effects (38). It is well established that to induce the remission of severe systemic vasculitis or connective tissue disorders, higher doses of methylprednisolone have the advantage of exploiting the non-genomic effects within seconds or minutes via biological membranes (36). This strategy could indeed be useful in patients with hyper-ferritinaemia and elevated biomarkers of inflammation such as CRP. Several reports suggest that methylprednisolone pulse could be an effective therapeutic approach for patients hospitalised with severe COVID-19 (39-42). Ruiz-Irastorza *et al*. analysed the effects of methylprednisolone pulses during the second week of disease in patients with severe COVID-19 pneumonia in comparison with standard of care (SOC) in relation to death, time to death or endotracheal intubation. The authors found that the pulses were effective in improving the prognosis of severe COVID-19 patients and suggested that this high-risk popu-

lation should be promptly treated with methylprednisolone pulses (43).
In conclusion the cautious use of glucocorticoids adopted at the beginning of the outbreak has now been surpassed. However, it is advisable to define more clearly how to optimise corticosteroid therapy moving towards more personalised interventions.

Targeted therapies: when and where can they be useful in COVID-19?

The novel insights in COVID-19 pathogenesis and the experience acquired in daily practice have modified not only the attitude towards the use of corticosteroids, but also the indications and the usage of several biological agents.

Tocilizumab

Since the beginning of pandemic, starting from pathophysiological and real-life evidences, Tocilizumab (TCZ), targeting IL-6R, seemed to have a crucial role in the treatment of severe COVID-19 pneumonia (44-46).
Until May 2020, hundreds of cases of COVID-19 patients treated with TCZ had been reported in the literature with promising results (46, 47); therefore, several clinical trials have been designed in order to evaluate its safety and efficacy.
Unfortunately, disappointing results have recently emerged from the first 3 randomised control trials (RCTs) (48-51), thus clipping the wings of physicians fighting COVID-19. These studies failed to demonstrate a significant efficacy of TCZ in patients with SARS-CoV2-induced pneumonia, in terms of reduced need for mechanical ventilation or death within 28 days; rather in a recent RCT, TCZ even seemed to increase the risk of 15-day mortality (52).
However, there are many reasons that can explain RCT failure, including the heterogeneity of the patients and the different timing of TCZ administration with respect to the onset of the disease. In fact, growing real life data and observational studies (53-58) on large cohorts of COVID-19 patients support the use of TCZ in severe cases, in addition to SOC (hydroxychloroquine ± antiviral therapy ± steroids) (59). These studies agree in highlighting that the hyperinflammatory state (CRP >150 mg/l), rather than the severity of respiratory parameters, and need for oxygen supplementation, represent the best predictor of anti-IL6R treatment response. So, these data suggest selecting the ideal candidates to TCZ therapy when an increase of inflammatory biomarkers (CRP more than D-dimer and lymphopenia) occurs (57).
It is currently accepted in the rheumatology literature that there is a "window of opportunity" for the appropriate timing and the use of targeted therapies in systemic autoimmune inflammatory diseases.
Growing evidence from the literature has answered our question, underlining that an ideal "timing" for TCZ treatment does exist and it seems to be short. Several authors have actually demonstrated the efficacy of anti-IL6R treatment (intravenous -iv- or subcutaneous -sc-) in reducing mortality, when administered early during the disease course, after the viral phase. In particular, the optimal timing seems to be within the 12° day since symptom onset or at least within the first days since Intensive care Unit (ICU) admission, especially in patients without mechanical ventilation and/or severe ARDS (P/F >250) (60-63).
Interestingly, the early identification of the inflammatory phase and correct therapeutic window may also allow a dose reduction of TCZ, while preserving the therapeutic efficacy. In this regard, three studies have obtained promising results with low-dose TCZ, both iv and sc, in addition to SOC (64-66), in patients who did not require ventilatory support, but with increased inflammatory biomarkers (67-70).

JAK1/2 inhibitors

The potential usefulness of JAK1/2-inhibitors, particularly baricitinib, for the treatment of SARS-CoV2 pneumonia has been already reported (71). Although this drug received less resonance in the scientific community, its clinical efficacy has been proven initially in 12 treated COVID-19 patients (72), and then in 113 moderate (median P/F 265 IQR 202-330) disease treated in the early phase (within 7 days since symptom onset) with baricitinib 4 mg daily for 14 days (plus SOC with lopinavir and ritonavir). The baricitinib-treated group showed a significant improvement within the first 2 weeks in terms of clinical, laboratory and respiratory functions with a reduced need for ICU admission and length of hospitalisation. These results were not obtained in the control group of 78 subjects treated with hydroxychloroquine (HCQ) (plus SOC). Moreover, in the group treated with baricitinib there was a lower percentage of persistently nasopharyngeal swab (NPS) positivity at 2 weeks than in the control group (12.5% *vs*. 40%, p=0.04), confirming the anti-viral effect of baricitinib (73). More recently, it has been proven that baricitinib counteracts the propagation of the virus in epithelial cells, via its inhibitory activity on the NAK family members (AAK1 and GAK) (74).
On the other hand, the beneficial effect of baricitinib on the response of the host's immune system is confirmed in a small group of patients (75) who experienced not only a reduction in the levels of inflammatory cytokines (IL-6, IL-1β, TNF-α), but also a rapid recovery of circulating T and B cells with a significant increase in the production of antibodies against SARS-CoV2, compared to patients treated with SOC (HCQ and/or lopinavir/ritonavir). This is probably due to the ability of baricitinib to restrain the immune dysregulation in COVID-19 patients, via its direct effect on the STAT3 pathway (76).
Taken together, these recent results support the use of baricitinib as an effective intervention strategy to inhibit the cytokine storm, but also to reduce host cell spread infection in COVID-19 patients. Therefore, based on clinical and laboratory observations, baricitinib may represent a promising effective and safe therapeutic strategy in the early phase of COVID-19, in order to prevent the hyperinflammatory response and the rapid evolution towards the severe respiratory failure.

Anakinra

IL-1-inhibition with high-dose anakinra is currently being evaluated as

a plausible treatment for COVID-19 since IL-1α is an important effector cytokine of innate immunity and is produced in the early phase of COVID-19. In this setting, the results of recent prospective and retrospective small cohort studies suggest the potential effect of anakinra at high dosage in patients with moderate-to-severe disease (77, 78). In addition, a high dose (100 mg every 6 hours) of subcutaneous anakinra was not inferior to TCZ in the resolution of acute respiratory syndrome (PaO2/FiO2 <300) in a small cohort of COVID-19 patients with serologic features of systemic hyperinflammation, as assessed by ferritin, IL-6 and D-dimers levels (79). Moreover, anakinra is often efficacious within hours, has a short half-life with wide therapeutic margin and is considered safe, not reducing the immune system capacity to viral clearance. Actually, a number of ongoing RCTs on anti-IL-1 therapy will further clarify its potential optimal use in the therapeutical armamentarium of severe COVID-19.

At present, anakinra (as well JAK1/2 inhibitors) appears to have the best safety profile to be used in combination with corticosteroids in order to maximise their anti-inflammatory effects, particularly in severe COVID-19 patients (80).

Other anti-rheumatic therapies: what is cooking in the kitchen?

Hydroxychloroquine

The broad anti-viral, anti-thrombotic and anti-inflammatory effects of HCQ supported heavy use of this drug in subjects affected by SARS-CoV2 infection, especially in the first phase of pandemic (1, 2). However, in the last months, the potential benefit of HCQ has been debated and strongly discouraged by treatment guidelines. In particular, in contrast with initial data from observational studies, the results of recent RCTs showed no benefit of HCQ in reducing symptom severity, mortality or improving clinical status both in outpatients and hospitalised patients with early or mild-to-moderate COVID-19 (80-84). Taken together, the results of RCTs suggest that HCQ is marginally or not effective for the treatment of COVID-19, regardless of the disease stage and the dose administered. Moreover, the high prevalence of cardiac adverse effects and the possibility of excess mortality risk reported in patients randomised to HCQ raised significant concerns on drug safety in these patients. Consequently, the FDA suspended the prescription of this drug except in the setting of clinical trials.

Indeed, HCQ has been used for decades by the rheumatologic community to treat chronic autoimmune diseases with an excellent safety profile. In this setting, the reasons for data discrepancy and drug failure in patients with SARS-CoV2 infection are complex and multifactorial (85). The marked variability and severity of COVID-19 disease phenotype and the complexity of the immune system activation may result in unpredictable responses to the same HCQ regimen. This suggests the need to identify the optimal disease phase and the subgroups of COVID-19 patients who may achieve the best efficacy with HCQ administration during infection. Importantly, the short-term dosing, not achieving enough tissue drug concentration, may represent an adjunctive major reason for drug failure. In this setting, using high doses to rapidly achieve high plasma concentrations may likely result in adverse effects and cardiac toxicity, not commonly seen at typical rheumatologic dosing.

Summarising, the available data do not currently support any effectiveness for HCQ as treatment or prophylaxis for COVID-19. The limited number of well-powered observational studies, the heterogeneity of patients analysed and the poor evidence from RCTs suggest that the current data on the efficacy of HCQ in reducing mortality among COVID-19 hospitalised patients are not conclusive. Well-powered RCTs are surely needed to assess the preventive and therapeutic effects of HCQ on asymptomatic, mild, and severe patients with COVID-19.

Colchicine

Colchicine has an effect on NLRP3 inflammasome, thus reducing the synthesis of IL-1β/IL18 and other pro-inflammatory cytokines. Moreover, colchicine hampers platelet-aggregation, which prevents microvascular thrombosis, and leucocyte migration through up-regulation of adhesion molecules (86). In addition, it has anti-viral activities with no immunosuppressive effect and is an inexpensive drug. These broad properties prompted the evaluation of the anti-inflammatory effect of colchicine in COVID-19 (87). A recent case-control study demonstrated the good safety profile and better efficacy of colchicine (1 mg/day) added to SOC in comparison to SOC alone in reducing mortality in a wide cohort of hospitalised patients with pneumonia (88). Moreover, these data have been confirmed in a prospective, open-label RCT where the colchicine treated group (1.5 mg + 0.5 60 min later, thereafter 0.5 bid) achieved significantly improved time to clinical deterioration compared to patients treated with SOC alone (89).

Undoubtedly, the use of colchicine in terms of dosing and timing of treatment represent two critical points to be considered (90). In acute gout attacks, colchicine is only effective at a high dosage. Indeed, while low-dose colchicine prevents neutrophil adhesion, only high dosages achieve the anti-inflammatory effect by shedding of L-selectin from neutrophils and preventing their further recruitment (91). If so, these preliminary results emphasise that the putative optimal timing of colchicine administration is in hospitalised patients with mild-to-moderate COVID-19 before any ventilatory support or ICU admission. Several RCTs have been planned to confirm these preliminary results in the early/intermediate phases of COVID-19 (NCT04375202, NCT04322565, NCT04355143, NCT04360980, NCT04350320, NCT04326790, NCT04328480, NCT04367168, NCT04363437, NCT04322682). Finally, a phase 3 study promoted by the Italian Society of Rheumatology (SIR) and the Italian Society of General Medicine and Primary Care (SIMG) aimed to evaluate the efficacy of colchicine in reducing the rate of hospitalisation in symptomatic outpatients (EudraCT2020-001806-42).

Anti-TNFs

The potential role of anti-TNF-α therapy deserves consideration. Indeed, it is known that anti-TNF therapy rapidly decreases IL-6 and IL-1 production and prevents leukocyte migration to inflamed tissues. However, clinical data on anti-TNF-α therapy in patients with COVID-19 are lacking. Currently, an open-label RCT aimed to assess the efficacy and safety of adalimumab in patients with severe COVID-19 pneumonia has been registered in the Chinese Clinical Trial Registry (ChiCTR2000030089) and an open-label, single-arm, phase 2 trial evaluating the efficacy of a single infliximab infusion in time to improve oxygenation in hospitalised patients with severe or critical infection is still recruiting (NCT04425538). Probably, major concerns about a possible increased risk of bacterial or fungal infections following anti-TNF-α therapy in these patients and the widely different half-life of this class of drugs has considerably limited their use to date (92). Clinical data suggest that patients treated with TNF-α inhibitors for inflammatory bowel diseases do not have a worse outcome of COVID-19 than those treated with conventional drugs. Use of anti-TNF-α therapy in these patients has been recommended in the case of moderate disease, as soon as possible after their hospital admission (92).

Interferons

In recent months, IFN-α and -β emerged as potentially therapeutic arms against SARS-CoV2 infection due to their anti-vital activity in the early phase. An open-label, randomised trial evaluated subcutaneous IFN-β1a (three times weekly for 2 weeks) in severe COVID-19 patients did not demonstrate any differences in the primary outcome of time to clinical response between the IFN treated and the control group, as well as in overall length of hospital stay, ICU stay or mechanical ventilation (93). In this setting, IFN-β1a may be beneficial if used early after hospitalisation in addition to anti-viral therapy (lopinavir/ritonavir and ribavirin) (94). Besides the putative beneficial effect of INFs (95), major adverse events (haematological and liver toxicity, depression and suicidal ideation) strongly limit the potential use of these drugs in COVID-19 treatment.

The impact of COVID-19 on the outcomes and management of patients with rheumatic musculoskeletal diseases

Since the last update (2), the most urgent and most investigated clinical questions on the relationship between COVID-19 and immune-mediated rheumatic musculoskeletal diseases (RMD) focused on: i. the incidence of COVID-19 in RMD; ii. the severity of COVID-19 in RMD; and iii. the identification of determinants of adverse outcome in RMD, with particular interest in immunomodulating and immunosuppressive drugs. These three groups of questions are closely interrelated and share potential methodological pitfalls to consider when interpreting the results (Fig. 1).

The incidence of COVID-19 in these diseases directly depends on the probability of infection which is influenced both by intrinsic individual susceptibility and by the exposure to potentially infected people. Several preventive measures impact on the risk of infection including hygiene measures, physical distancing, use of protection devices, home working until strict isolation. A Dutch study showed that, during the first wave of the COVID-19 epidemic, RD patients were almost twice as likely to adhere to strict isolation measures when compared to healthy controls (odds ratio [OR] 1.8, 95% CI 1.5–2.4) (96). In this perspective, the incidence of COVID-19 in RD patients should relatively decrease compared to the general population. Nevertheless, a recently published meta-analysis of controlled studies suggests a global increase in the diagnosis of COVID-19 in RD patients, with a 1.59 pooled odds ratio (95%CI 1.13, 2.25) (97). When analysing by meta-regression the main factors associated with higher prevalence of COVID-19 in RD patients, glucocorticoids showed a significant association with a diagnosis of COVID-19, while age, gender, comorbidities and c/b/ts-DMARDs were not associated with different risks. Despite these results, it is not possible to identify the relative contribution of a potentially increased susceptibility beyond prevention in RD based on the available evidence.

A further level of complexity is related to patients with asymptomatic SARS-CoV-2 infection. When measured by the positivity of a specific test outside a screening program, incidence is related to the propension to test a particular group of patients. A population-based study on healthcare administrative databases, carried out within the Reggio Emilia area in Italy, pointed out that patients with bDMARDs or ts-DMARDs were more likely to be tested compared to the overall population (about 40% higher probability of testing) (98). If patients with immune-mediated RMD are more likely to be tested because of the fear of severe diseases, the incidence would be inflated in this group of patients with relatively more patients with a mild disease who will not be tested if not at high risk. This bias may decrease the estimated of severity of COVID-19 in RMD. Based on the available data of 289 patients compared to the general population from Italy (98), Spain (99) and the USA (100), the pooled risk of severe outcome was not significantly increased in immune-mediated RMD patients: pooled OR of hospitalisation of 0.87 (95%CI 0.62–1.23) and pooled OR of death of 1.43 (95%CI 0.89–2.31) (97). However, the lack of information on the general population of infected people rather than of the tested one does not allow drawing reliable conclusions. Furthermore, RMD are a heterogeneous group of diseases, with huge differences in demographic structure, organ involvement and treatment. For this reason, the investigation of the determinants of severe outcome in RMD is critical in order to understand the profile of patients with higher risk, including potentially harmful treatments. The first results of the COVID-19 Global Rheumatology Alliance (GRA) database has identified the risk factors for hospitalisation in patients RD and COVID-19, based on NPS, serology or clinical diagnosis (101). Analysing the first 600 patients, with 46% of hospitalised patients, the major general deter-

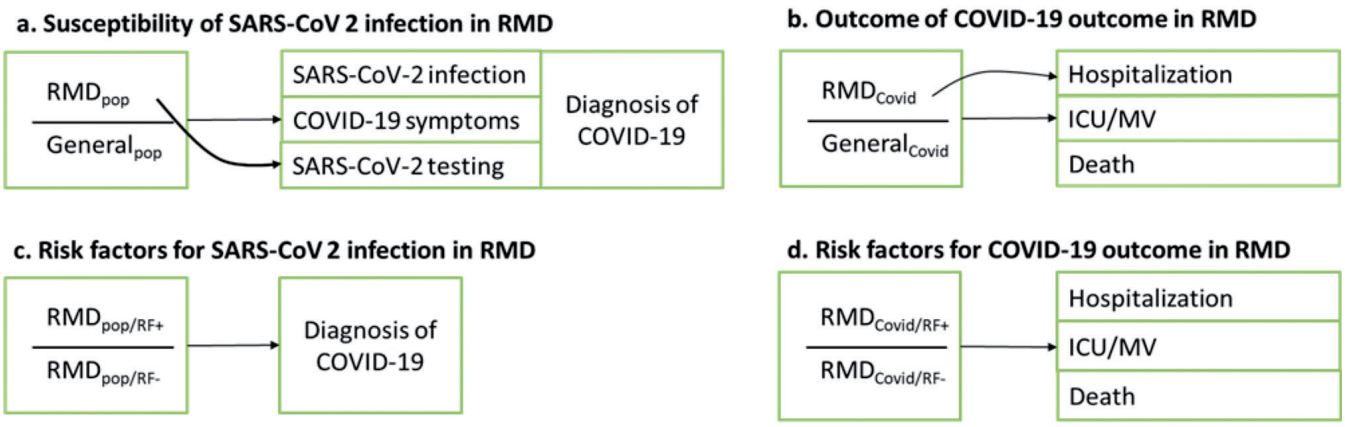

Fig. 1. Clinical questions on the relationship between COVID-19 and RMD and potential biases. Straight lines refer to the relationship of interest between exposure and outcome. Curved lines refer to potential biases. In panel **a**. RMDs may affect the probability of testing for SARS-CoV 2, leading to an overestimation of the susceptibility; in panel **b**. RMDs may increase the probability of hospitalisation independently from the severity of COVID-19, leading to the inflation of the severity estimates. Research questions applied to the RMD population alone (panel **c**, and **d**) are not influenced by major biases.
RMD: rheumatic and musculoskeletal diseases; ICU: intensive care unit: MV: mechanical ventilation; RF: risk factor (+ present, - absent).

minants of hospitalisation included age, comorbidities (particularly cardiovascular, pulmonary, diabetes and CKD), as expected for the general population. Among RMD variables, DMARDs (conventional or b/ts DMARDs) and NSAIDs did not show an increased risk of hospitalisation, with even a reduction of the risk in b/ts DMARD monotherapy (0.46 (0.22–0.93). Conversely, a medium-high dose of glucocorticoids (>10mg PDN-equivalent/day) increased the risk two-fold (2.05 (95% CI 1.06–3.96)). No differences were found regarding antimalarials and disease activity in univariable analyses. A more recent analysis from the Italian Register of COVID-19 in RMD (CONTROL-19 database), promoted by the SIR, analysed 232 RMD patients with RT-PCR confirmed COVID-19 (102). The analyses of the association of treatment and a composite index of adverse outcome (ICU admission, mechanical ventilation of death) confirmed the general safety of cs/b/ts-DMARDs, with a potential increase of the risk for glucocorticoid users. The result of a meta-regression of studies analysing death as the outcome measure supports these results. Cs-DMARDs were associated with worse outcome while b/ts DMARDs with a better outcome, in particular TNF-I, with an increase not statistically significant for glucocorticoids. The potential protective effectiveness of these drugs should be interpreted with caution because of the potential channeling bias, not fully controlled by the analyses, leading to treatment with b/ts-DMARDs for patients with lower comorbidity burden, while the association between glucocorticoids and severe outcomes should be assessed with more powered analyses. Beyond these general data, more specific reports support the hypothesis that RMD with organ involvement, such as connective tissue disease (99), as well as treated with major immunosuppressants, may be associated with a worse prognosis (103). At present we know that the susceptibility of COVID-19 does not seem to be decreased in RMD, and only a population-based, or hospital-based serology study would fully respond to this question (104). Using this definition of case, we will be able to understand the severity of the disease in this subgroup of patients, while the existing database of COVID-19 in RMD will answer relevant questions on the subgroup of high-risk patients. Future studies will uncover the long-term consequences of the COVID-19 pandemic on the management and outcome of RMD patients. The COVID-19 pandemic has raised several organisational challenges related to the management of RD. The unexpected outbreak has implied that healthcare systems had to reorganise themselves in order to respond to this global pandemic at different levels; in fact, one of the main challenges was represented by the reorganisation of care needed to manage COVID-19 patients and a consequence of this was that non-COVID-19 units experienced a significant lack of resources (105). Unfortunately, many of these units were taking care of rheumatic patients, therefore most of their activities were temporarily reduced or interrupted in order to be dedicated to COVID-19 care, including the suspension of inpatient and outpatient clinics, or provision of infusion therapies. This resulted in a discontinuation or delay of care for rheumatic patients who, in many cases, were not able to access their healthcare provider or were not able to undergo the monitoring exams needed for an adequate follow-up of their disease. In addition, several health-care professionals observed an increased number of disease relapses due to the interruption of the pharmacological therapies by the patients themselves, or reluctancy to initiate a new immunosuppressant therapy for its potential noxious negative effects in case of COVID-19. Switching rout of administration from infusion to subcutaneous injections was a possible solution to reduce access to the healthcare provider when not strictly necessary, however, the impossibility to perform face-to-face evaluation represented a big challenge in any case (106, 107). As far as the discontinuation of care is concerned, one of the proposed solutions was the use of telemedicine, consisting of phone calls, video calls or email-based consultation (108, 109). What can we say regarding this inno-

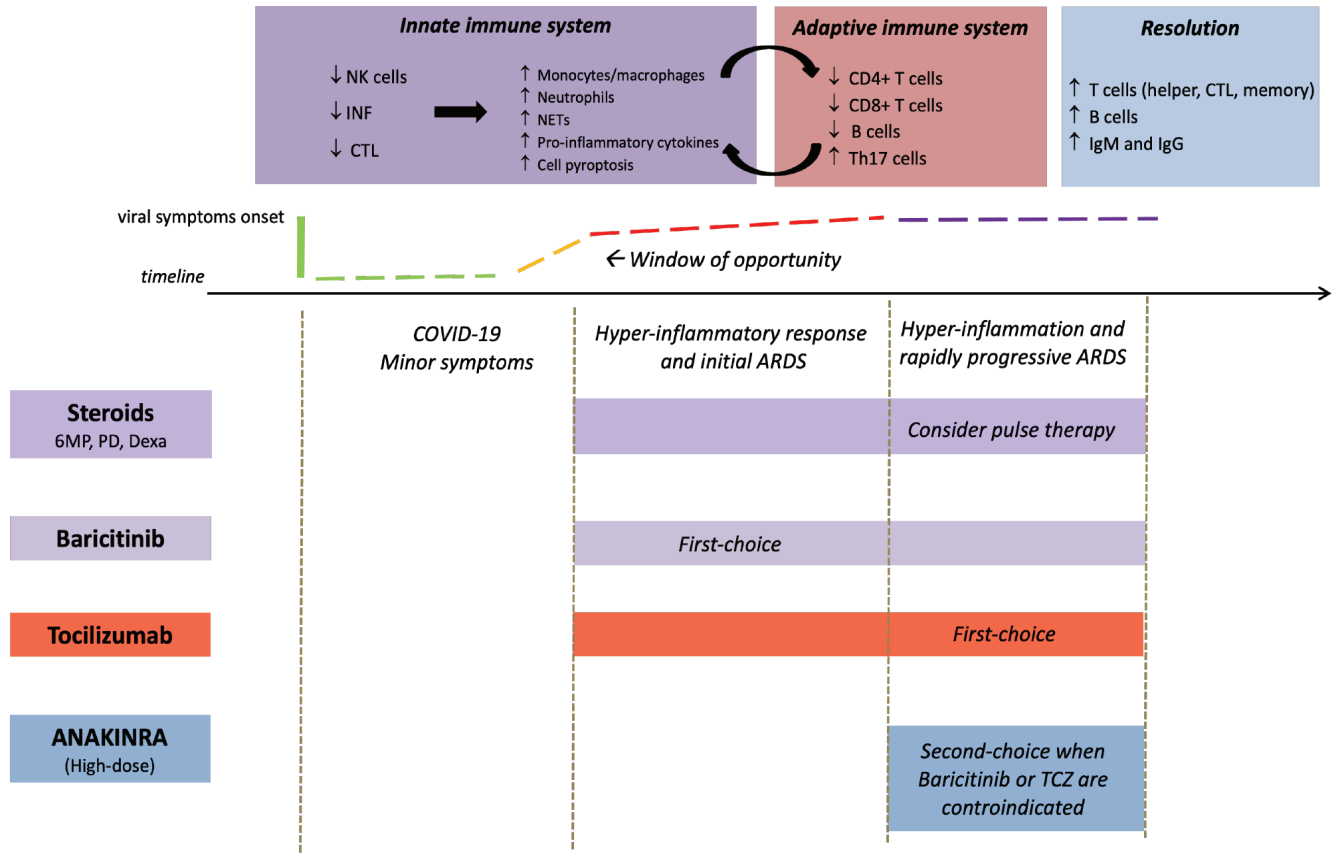

Fig. 2. Updated algorithm on therapeutical approaches in COVID-19 based on the present knowledge of the pathogenesis of COVID-19, literature data and our personal experience. NK: natural killer cells; INF: interferons; CTL: cytotoxic T lymphocytes; NETs: neutrophil extracellular traps; MP: methylprednisolone; PD: prednisolone; Dexa: dexamethasone; TCZ: tocilizumab; ARDS: acute respiratory distress syndrome.

vative approach in the clinical management of RD after several months from the COVID-19 outbreak? Telemedicine has been and will continue to be a valuable tool for monitoring rheumatic patients, especially for the identification of patients needing immediate care, like a kind of 'triage' of different clinical or therapeutic problems when other options are not available. However, face-to-face evaluation remains essential in patients with systemic autoimmune diseases, in order to perform an appropriate control of disease relapse, to improve adherence to treatment and to prevent patients from perceiving themselves as being alone. Thus, it is desirable that specific organisational strategy health plans are designed in order to guarantee the continuity of care for rheumatic patients even in the event of future health emergencies.

Conclusions

There is no doubt that COVID-19 is a new challenge for rheumatologists. First, at the beginning of this pandemic we ignored the impact of this viral infection on the activity, progression and outcome in our patients, particularly in those with autoimmune inflammatory disease undergoing complex immunosuppressive anti-inflammatory therapies.

One year later, growing evidence derived from national or international registries has clarified that COVID, with some exceptions, did not significantly modify the management of these diseases. However, the restrictions imposed by this pandemic, the reluctance of patients to go to hospitals, combined with the reorganisation of our clinics, have profoundly compromised the standard of care and the monitoring of our patients. We therefore faced an initial delay in the new diagnosis and in many instances the discontinuation of therapies, due to poor compliance, uncertainty of the potential noxious effects of our immunosuppressive anti-inflammatory regimens on the outcome of COVID and, last but not least, to the temporary lack of some drugs, such as HCQ or tocilizumab, which suddenly became popular in the off-label use of COVID-19.

To overcome these difficulties, it was necessary to reorganise our clinics with the use of telemedicine. In this regard, the progress reached in this procedure may certainly be important in the future reorganisation of our clinics at the end of the pandemic.

On the other hand, as outlined in our first editorial a year ago, the similarities between the pathogenetic mechanisms underlining the "cytokine storm" of COVID-19 with virus-induced or idiopathic systemic autoimmune inflammatory RD prompted the use of the therapeutic armamentarium currently used, often exclusively, for the management of this latter condition.

Over the years, we, as rheumatologists or clinical immunologists, have learned some basic concepts in the management of these diseases:

1. No single drug or fixed dose is able to treat all the systemic manifestations;
2. Any drug has specific indications according to the stage of the inflammatory process;
3. In many cases the association of multiple synthetic and/or targeted therapies is necessary;
4. A more precise knowledge of the pathophysiological basis of the disease and the mode of action, side effects and interactions of the different drugs, and the awareness of the concomitant comorbidities are necessary at any time to select the putative ideal therapy in the individual patient;
5. The identification of appropriate parameters is necessary to monitor the effectiveness and safety of any treatment protocol and the prevention of irreversible damage.

Based on these considerations, in our first articles (1, 2) we outlined that similarly to the systemic autoimmune diseases, a "window of opportunity" exists for the appropriate therapy in the different stages of COVID-19.

As discussed previously, our hypothesis one year later has received confirmation of the efficacy of corticosteroids but yielded less definite or conflicting results with the use of the other synthetic or targeted therapies. This can easily be explained by:

1. Differences in the study protocols due to the use of the same drug in different dosages and stages of the disease;
2. The difficulty in designing appropriate prospective controlled studies in the absence of standard background therapies;
3. Incomplete knowledge of the pathophysiology of the disease and lack of reliable parameters capable of monitoring the disease and predicting its outcome;
4. The extreme heterogeneity of the clinical skills involved in the treatment of these patients worldwide.

At the same time, as physicians at the bed-side of these patients, we have learned how difficult it is to use "the one-size fits all" approach to face the multiple aspects of COVID-19, particularly in those patients with other concomitant comorbidities, and how the experience previously acquired on the use of these drugs has helped to successfully manage individual critical cases.

Figure 2 is an updated algorithm based on the present knowledge of the pathogenesis of the disease, the data of the available literature and, last but not least, our personal experience acquired this year at the bedside of patients with COVID-19.

Finally, these months have strongly convinced us that while waiting for a definite effective vaccine, a structured multi-disciplinary approach is necessary in the individual hospitals to optimise the treatment and follow-up of these patients over time.

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