Editorial

COVID-19: the new challenge for rheumatologists

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On Saturday, March 21, 2020 two articles on coronavirus disease 2019 (COVID-19) were submitted to *Clinical and Experimental Rheumatology*: a review by the colleagues from Milan, summarising the current knowledge on this new disease, and a letter on the same topic from Portugal (1, 2).

We have given these articles top priority not only because of their topic, but also because the review was submitted by the principal hotspot in Italy (and probably in the world in this moment) where the epidemic is more serious. This article testifies that our colleagues, although on the forefront at the bedside of their patients, also wanted to share their expertise with scientists all over the world to help identify potential solutions.

Another significant aspect is that it derives from the active collaboration between rheumatology and infectious diseases specialists. While this new epidemic found the scientific community totally unarmed towards this new virus, it became immediately clear that among the unproven remedies tested, some of the most promising were well-known drugs used by rheumatologists, such as hydroxychloroquine and tocilizumab, and that our expertise may be useful in understanding the mechanisms underlying this disease, thus contributing to reach a possible solution.

While waiting for more solid scientific evidence, we have tried to summarise some of the questions that have risen from the needs of our patients. At the same time, we have also tried to formulate some hypotheses that could possibly shed light on explaining the potential benefits and/or side effects in the use of these drugs, currently used in systemic autoimmune diseases, in the management of COVID-19.

Is COVID-19 just an infectious disease or something else?

Although it remains to be elucidated how severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2) interacts with host antiviral immunity, lessons can be learned from other HCoVs and human pathogenic viruses. Sarzi-Puttini *et al*. analysed the crucial role of the immune system during COVID-19 in comparison to SARS and Middle East respiratory syndrome (MERS), acute respiratory diseases caused by similar coronaviruses and associated with high morbidity and mortality rates (1). Low levels of antiviral cytokines, particularly type I interferons (IFNs) seems to share COVID-19 with SARS and MERS. Interestingly, the authors hypothesised that the decrease in INF-γ may suppress Th1 and favour Th2 responses. This is an intriguing hypothesis, but needs to be confirmed. In fact, dysregulation in the balance between Th1 and Th2 lymphocytes must be demonstrated by an increase in Th2-derived cytokines such as IL-4, IL-13 and IL-5 in both sera and lung tissue. In light of the data on lymphopenia observed in COVID-19 as well as in SARS and MERS, it would be necessary to deeply analyse subpopulations of T lymphocytes in the different stages of the disease, paying particular attention to any changes in the T regulatory lymphocytes (Treg). Dysregulation in different T cell sub-types can lead to a failure of the adaptive immune system with possible negative effects on B lymphocytes and on their antibodies production. The increase in pro-inflammatory cytokines, in particular IL-6, associated with severe pneumonia can have deleterious effects on the adaptive immune system, as Sarzi-Puttini *et al*. have correctly pointed out (1). We must

also stress that the "pro-inflammatory cytokine storm" is only the tip of the iceberg. In order to add other pieces to our current knowledge on the inflammatory milieu in course of COVID-19, it would be interesting to analyse other cytokines belonging to the IL-1 family, including both pro-inflammatory and anti-inflammatory ones, their soluble receptors, some of which act as inhibitors of signalling, and molecules regulating their activity such as caspase-1 and inflammasome components.

In light of the new immunological findings it would be relevant to investigate in parallel to T lymphocytes the potential role of the newly described Innate Lymphoid Cells (ILCs), their different phenotypes and their contribution to the host immune defenses in COVID-19. Last but not least, future genome-wide association studies (GWAS) or independent replication studies are required in order to identify potential genes associated with susceptibility to develop more severe form of COVID-19 and their link with defects of the host immune responses.

Is there a "window of opportunity" for anti-rheumatic drugs in COVID-19 patients? Is there room for sequential/combined therapy?

Sarzi-Puttini *et al*. indicated in their review a list of possible anti-rheumatic drugs that can be useful in COVID-19 patients, extensively discussing the rationale of their employment (1). In this scenario many questions arise on the basis of the experience gained in rheumatic diseases. The first question concerns the possibility of being able to identify a "window of opportunity" considering that an earlier intervention may increase the possibility of a better outcome. Other key concepts, derived from the rheumatology experience, including the hypothesis of "sequential therapies" or "treatment combinations" might be considered in the near future to balance the risk of infections and the treatment efficacy. Similarly, the concept of "treat-to-target" should be stressed in order to improve the general knowledge regarding biomarkers that may help to identify the right therapy for the right patient. As far as new insights will come out emphasising the crucial role of innate immunity dysregulation and cytokine storm in the disease progression, other "old drugs" used in autoinflammatory disorders, including colchicine, might enter in our therapeutic algorithm. In this perspective, the Italian Society of Rheumatology (SIR), the Italian Society of Infectious and Tropical Diseases (SIMIT) and the Italian Thoracic Society (AIPO) have recently promoted an open-label, phase-2 study on patients with COVID-19 in order to evaluate the efficacy and safety of colchicine treatment. This trial ("Treatment with COLchicine of patients affected by COVID-19: a Pilot Study – COLVID-19") is currently under evaluation by the Italian Medicines Agency (AIFA).

It is of course difficult to provide solid answers to all the above questions at present; however, hopefully, novel insights into the disease pathogenesis and clinical manifestations will help us to improve our strategies.

The role of tocilizumab in the management of SARS-CoV2: which is the "window of opportunity"?

As Sarzi-Puttini *et al*. have pointed out in their review, the clinical presentation of COVID-19 infection might be extremely heterogeneous and TCZ seems to have a crucial role in the therapeutic armamentarium of the disease (1).

Considering the rapid evolution of systemic and lung inflammatory life-threatening involvement, it appears of utmost importance the early identification of clinical and biochemical markers, expression of the secondary hyper-immune response mainly related to the monocyte-macrophage system activation.

According to recent data from the Chinese cohorts, patients with severe disease and in need of the intensive care unit (ICU), compared to patients with mild disease, often show leucopenia, lymphopenia, thrombocytopenia, hypo-albuminaemia and significantly higher levels of C-reactive protein (CRP), thrombin time, fibrinogen, glucose, lactic dehydrogenase (LDH) and transaminases. Moreover, higher levels of IL6 (>24.3 pg/mL) and D-dimer (>0.28 μg/L) were predictive of the development of severe pneumonia in COVID-19 patients, with a sensitivity of 93.3% when the two parameters were combined by parallel testing (IL6 or D-dimer) and a specificity of 96.4% when using a tandem testing (IL6 and D-dimer) (3, 4). It is likely that ongoing RCTs will help to refine the sensitivity and specificity of these candidate biomarkers of patients that should be treated earlier and more aggressively. In the scenario of moving towards an early diagnosis, we have to bear in mind that data from Chinese hospitalised patients showed that the median time from illness onset (first COVID-19 symptoms) and admission to ICU, with necessity of mechanical ventilation, is 10.5 days, after a median of 1.5 days from acute respiratory distress syndrome (ARDS) diagnosis and 2.5 days from dyspnoea onset (4). "Silent hypoxemia" (without severe dyspnea), occurring especially in elderly patients, and the rapid evolution of lung findings at CT scan make the identification of the "window of opportunity" particularly challenging for clinicians (5-7). Therefore, lung ultrasound (LUS) is being confirmed an extremely useful tool for the management of SARS-CoV as a bedside feasible, repeatable, radiation-free tool with high sensitivity and specificity for early, pre-clinic and rapidly progressive lung involvement (8-10).

In conclusion, the detection of a rapid worsening of systemic and respiratory manifestations, some biochemical markers of inflammation, in particular IL6 and D-dimer levels, and a close LUS monitoring may represent a useful core set for the identification of the ideal TCZ-responder and the optimisation of the correct timing for drug administration. Further studies and ongoing clinical trials will help us to better define patients eligibility candidate to a more aggressive intervention as well as response and therapeutic biomarkers.

Is there a potential role for intravenous immunoglobulin (IVIg) in the management of COVID-19 infection?

Sarzi-Puttini *et al*. have shed new light on a high number of possible rheumatic drugs to be used in COVID-19

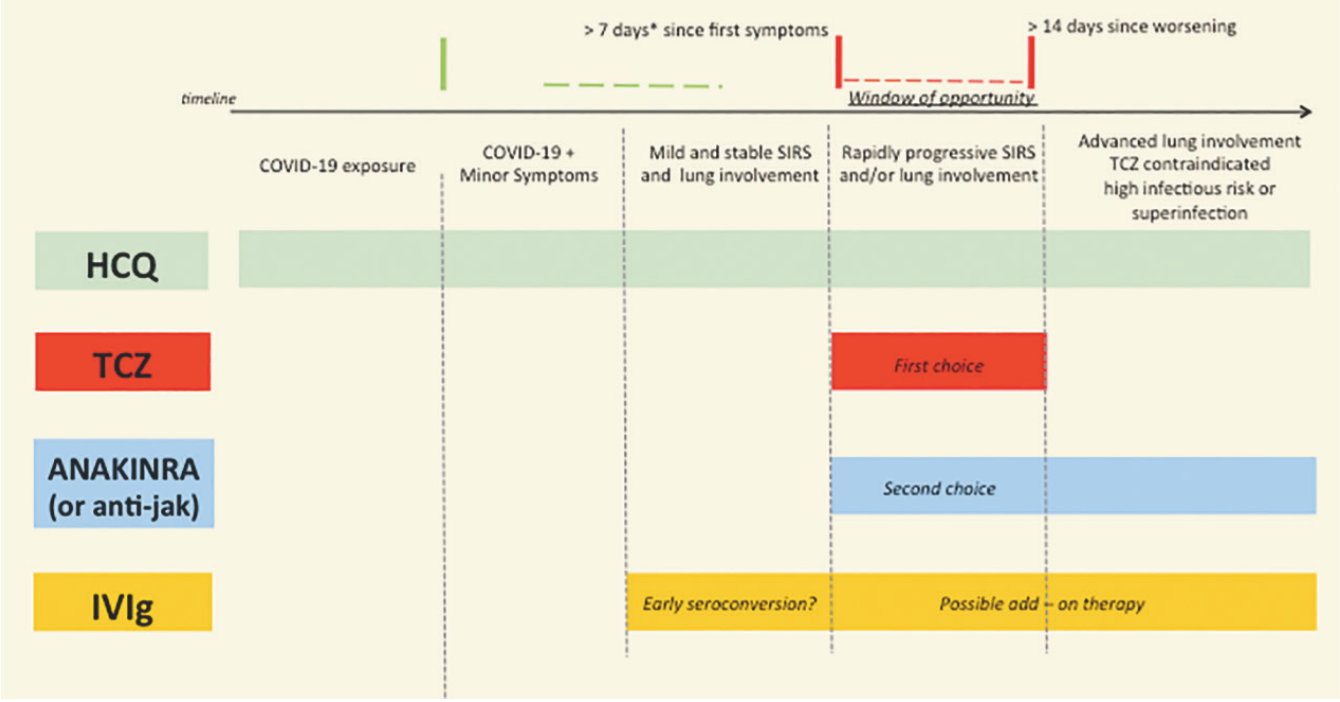

Fig. 1. Hypothetical timing of some anti-rheumatic drugs in COVID-19 infection.
*hypothetical viral load reduction.
HCQ: hydroxycloroquine; TCZ: tocilizumab; IVIg: intravenous immunoglobulin.

infection (1). In selected cases other rheumatic drugs may have a rationale of use, including IVIg. In fact, the COVID-19 virus seems to induce an inflammatory response due to macrophage hyper-activation especially in the lungs, through several mechanisms including interaction with membrane receptors for the Fc portion of the immunoglobulin (FcR).

Studies in animal models of SARS-CoV indicate that viral surface antigen S (Ag) and host antibodies (anti-Spike IgG) complex promotes the FcR-mediated internalisation of the virus in macrophages (antibody-dependent enhancement - ADE) and activates intracellular signalling of FcR. This interaction results in the up-regulation and release of the pro-inflammatory cytokines, responsible for severe lung and systemic complications (11, 12). Studies show that the development of acute respiratory symptoms during SARS-CoV coincided in 80% of cases with the serum conversion (anti-Spike neutralising IgG - anti-S Nab). In addition, deceased patients for SARS-CoV complications reached their peak levels of neutralising antibody activities after an average of only 14.7 days from the onset of symptoms, compared with 20 days in recovered patients (13, 14). Indeed, IVIg are quite expensive, but in selected cases they may represent a therapeutic strategy in patients with early seroconversion, in order to inhibit the FcR-mediated ADE and macrophages production of inflammatory cytokines.

Moreover, in line with the rheumatological experience, IVIg anti-inflammatory effect predominates over the immunosuppressive effect (15, 16) making IVIg treatment potentially useful in COVID-19 patients with bacterial superinfection and in conditions where the differential diagnosis between autoinflammatory/autoimmune disease and intercurrent infections is particularly difficult. Nevertheless, the high cost and the relatively low availability of IVIg may represent a limitation for the role of this therapeutic option in an epidemic viral disease, making it necessary to accurately select the target patients.

On the basis of the recent literature, Figure 1 summarises a hypothetical timing in the COVID-19 therapeutic approach, highlighting the concept of "window of opportunity".

Does adjunctive corticosteroid therapy have a role in the management of COVID-19 patients?

Sarzi-Puttini *et al*. pointed out that the effectiveness of adjunctive glucocorticoid therapy in the management of COVID-19 infected patients remains currently controversial (1). In line with this position, the WHO has recently advised not to routinely give systemic corticosteroids for treatment of viral pneumonia outside of clinical trials unless they were indicated for other reasons (*i.e*. exacerbation of asthma or COPD, septic shock) (17). To date, therefore, according to the current interim guidance from WHO, corticosteroids have been conditionally recommended only in patients with sepsis (including septic shock) (18). However, at the same time WHO has prioritised the evaluation of corticosteroids in clinical trials to assess safety and efficacy. Indeed, a great deal of data including animal experiments (19) as well as observational studies indicated that glucocorticoids may reduce inflammation, ameliorate lung injury and reduce mortality in critically ill patients with SARS similarly to what happens in patients with acute respiratory distress syndrome (20-23).

In particular, Tu *et al*. demonstrated that corticosteroids might attenuate acute lung injury by restoring the balance of macrophage subsets in the lungs (19). The authors demonstrated that corticosteroids promoted the differentiation of macrophage type 2 (M2) locally, which in turn induced more Tregs rather than the differentiation of pro-inflammatory macrophage type 1 (M1) which induced more Th17. Moreover, *in vivo* corticosteroids appeared able to reduce neutrophil chemokine IL-8, monocyte chemoattractant protein-1 (MCP-1), and Th1 chemokine IFN-gamma-inducible protein-10 (IP-10) that seem to play a crucial role in patients with SARS (24).

On the basis of the experience gained in systemic autoimmunity, a crucial unmet need is therefore to understand how to weigh up the likely adverse effects of corticosteroid therapy against the benefits likely to accrue from its utilisation.

From this perspective it has been widely recognised that effectiveness of corticosteroid therapy has been assessed by using different type of steroids and different regimens (*i.e*. high dose pulse - regimens *vs*. non-pulse regimens) in phenotypically different patients and in different phases of the disease. Therefore, several compelling questions regarding corticosteroid regimens and patients sub-phenotyping are still open. Hopefully, a new RCT recently registered by Zhou *et al*. that will compare methylprednisolone via intravenous injection at a dose of 1–2mg/kg/day for 3 days *versus* a control group not using glucocorticoid (ClinicalTrials.gov, ChiCTR2000029386) (25) will help to answer some of our questions in the near future.

Does immunosuppressant therapy for rheumatic diseases have a protective role against COVID-19 infection? Which drugs to withdraw, continue or start?

The recent outbreak of COVID-19, caused by the virus SARS-Cov2, has become a public health emergency of relevant international concern. Risk factors for poorer outcome include advanced age, male sex and concomitant comorbidities. Nevertheless, the complex and still unknown dysregulation of innate and adaptative host immune responses following COVID-19 infection represents a major concern also in subjects with a systemic immunosuppressive state caused by malignancy or immunosuppressive therapies, as in patients with systemic rheumatic diseases (26). Currently, however, the COVID-19 rate risk in immunosuppressed, in particular in subjects with chronic inflammatory and autoimmune disease, is still largely unknown. The analysis of past similar outbreaks of severe acute respiratory syndrome, as SARS-CoV in 2002 and MERS-CoV in 2015, and the recent epidemiologic studies on wide cohorts of patients with COVID-19, identified some risk factors for poor outcome, as advanced age, male sex and presence of comorbidities, including hypertension, obesity, diabetes, coronary heart disease, chronic obstructive lung disease and chronic kidney disease (27, 28). Immunosuppressed status was not found to be a risk factor and risk of adverse outcome, as death or admission in ICU, was not reported to be associated with chemotherapy or other conditions requiring immunosuppressive treatment. An encouraging message comes from a recent report that, among patients followed in a liver transplantation centre in Northern Italy for autoimmune liver disease or immunosuppressed for chemotherapy, none developed a clinical pulmonary disease, despite some tested positive for SARS-CoV-2 (29).

Nevertheless, in patients with chronic inflammatory and autoimmune diseases, we must consider, on one hand, that immunosuppressive treatments are essential to control disease activity and poorer functional status. On the other hand, we must not overlook the immunosuppressive effect of these drugs which may promote the spreading of COVID-19 infection. Lymphocyte subset analysis in patients hospitalised for novel COVID-19 revealed that SARS-CoV-2 mainly act on T lymphocytes, including helper T cells (CD3+CD4+), suppressor T cells (CD3+CD8+) and regulatory T cells, and that the decline of helper T cells was more pronounced in severe cases (30). In this setting, although some drugs commonly used in patients with rheumatic diseases, like leflunomide, may act by inhibition of T-cell proliferation, it is intriguing that they may also exert some antiviral effect. Moreover, the selective modulation of systemic inflammatory response or of specific cell subpopulations involved in immune pathogenesis of rheumatic diseases, may hamper selective viral responses. Both *in vitro* and *in vivo* studies demonstrated that chloroquine and hydroxychloroquine may exert a significant inhibition of viral replication and cell entry (31). Moreover, chloroquine can also act on the immune system through regulation of cell signalling and pro-inflammatory cytokine release, thus potentially controlling the "cytokine storm" associated with a poorer outcome in these patients (31). Similarly, biologic drugs employed in patients with rheumatic diseases modulate the immune response which, if uncontrolled, can be the direct cause of diffuse alveolar damage in patients with COVID-19 infection. In this setting, biologic drugs selectively blocking inflammatory cytokines, such as TNF-α inhibitors, anti-IL6, anti-IL1 and JAK inhibitors are currently employed in the treatment of severe cases of COVID-19. Of consequence, it may be hypothesised that the modulation of immune system induced by a chronic immunosuppressive therapy in patients with systemic rheumatic disorders may mitigate the burden of dramatic inflammatory response following COVID-19 infection. Moreover, stopping immunosuppressive therapy may worsen the disease and induce a systemic inflammatory state which may represent an adjunctive risk factor for major susceptibility to viral infection. In accordance, the American College of Rheumatology (ACR) (32), the European League Against Rheumatism (EULAR) (33) and the Italian Society of Rheumatology (SIR) (34) advise patients not to stop or reduce immunosuppressive therapy unless physician indication or presence of specific symptoms. Surely, waiting for data coming from international observational registries, strict follow-up of these patients is needed and detailed

information should be provided to aggressively implement infection control measures.

Will the era of COVID-19 change the screening of rheumatic patients candidate to start immunosuppressant therapy?

The outbreak of COVID-19 has become a public health emergency of major international concern and it is affecting the management of several chronic conditions, such as onco-haematological diseases (35). The complexity of this new problem is having also an important impact on the management of all patients taking immunosuppressive drugs for their autoimmune systemic diseases, not only for those already under treatment, but especially those who are about to start a new treatment to control their disease activity. In fact, significant research efforts will be required to better clarify the impact of each single conventional or biological DMARDs on the natural history of COVID-19 disease and on the outcome of this infection. In this COVID-19 era, registries and specific observational studies aimed at assessing the safety of our therapies are pressingly needed to answer this question.

What should we expect in the near future? Are we going to have to be even more careful in prescribing NSAIDs, steroids or DMARDs to our patients? Should patients who need to start conventional or biological immunosuppressive drugs be screened for potential COVID-19 infection? Are recurrent infections possible? In that case, might immunosuppressive drugs impact negatively on virus reactivation?

At the moment, we know that a specific screening should take place prior to initiating immunosuppressive drugs; this is the case for example of biological therapies that require prior screening for tuberculosis (TB), hepatitis B and C. Specifically, in all patients considering biologic therapy, screening should be performed to detect both active and latent TB infection (LTBI) since the anti-TNF-α treatment increases the risk of latent TB flare-up (36). Unfortunately, so far there are no data on the potential course of COVID-19 disease in rheumatic patients and more comprehensive studies are needed in order to know the percentage of subjects positive to the virus who will develop signs and symptoms of COVID-19.

To date, the principles of common sense have guided us in the management of patients undergoing new therapies that envisaged, after the usual diagnostic screening, isolation of 15 days for asymptomatic patients who were about to start a new treatment. In the case that the patient did not show any signs or symptoms related to COVID-19 infection, the new therapy could be initiated. More evidence may be collected when specific tests are available to detect active infections and to tell whether a person has been infected in the past; therefore, it is desirable that more evidence collected on rheumatic diseases patients and COVID-19 infection can allow the scientific community to develop specific recommendations that can guide the management of our patients, especially regarding pre-therapy screening. The one thing we know for sure so far is that this new scenario will have an impact on the management of many chronic conditions.

Conclusions

These are only some, and probably not the most important, questions that deserve to be addressed in order to solve this problem. As a rheumatology journal, we are therefore open to stimulate, from now on, a public debate and mobilise the best skills in order to be able to develop new original ideas. Never as in these times, has the medical and scientific community been asked to cooperate to win this difficult battle, which also represents for the rheumatologists the "challenge" for our near future.

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