Anakinra in COVID-19 therapy: what have we learned from adult-onset Still's disease?

Sirs,

Coronavirus disease 2019 (COVID-19) has recently assumed the proportion of a pandemia causing thousands of infections and deaths all over the world. The lack of a vaccination able to give a long standing-protection against SARS-nCov-2 has encouraged the use of a large number of therapeutic drugs with various target mechanisms. Among them, anti-inflammatory treatments have revealed an ability to control the viral-induced cytokine storm, which plays an important role in the pathogenesis of the disease.

It is now established that Coronavirus disease involves evolutive clinical phases, controlled by different pathogenetic mechanisms (1). The first phase, often paucisymptomatic with mild respiratory or systemic symptoms such as malaise, is sustained by the early establishment and viral replication in the host site of inoculation. In this phase antiviral therapy could give the best benefits.

The second phase is dominated by the inflammatory host response, both pulmonary and systemic, induced by the virus and driven by a cytokine burst which could lead to acute distress respiratory syndrome (ARDS), systemic inflammatory response syndrome (SIRS), macrophage activation syndrome (MAS), up to multiple organ failure (MOF).

This second setting often corresponds to patient hospitalisation due to the onset of major systemic symptoms such as fever, worsening asthenia and respiratory failure. Laboratory findings show increased levels of inflammatory indexes such as C-reactive protein, erythrocyte sedimentation rate, hyper-fibrinogenaemia and hyperferritinaemia, but also lymphopenia, abnormal levels of complementaemia and liver enzymes, hypergammaglobulinaemia, along with coagulation disorders in a pro-trombotic state. We notice that both clinical and serological features of this phase of COVID-19 strictly resemble the typical acute presentation of an adult-onset Still's disease (AOSD). Still's disease is a rare systemic inflammatory disorder to unknown aetiology presenting with a cluster of symptoms including fever, skin rash, arthritis/arthralgias, lymphoadenopathies, with fever and sierological manifestations of an hyperinflammed state often heralding the other manifestations.

We performed a revision of a single centre experience (*i.e.* patients referred to the Clinical Immunology Unit of the University of Pisa in the last decade), showing a total number of 42 patients (25 male; 17 female) with a diagnosis of adult-onset Still's disease in clinical follow-up (median follow up of 7.14 years, ±3.4). The symptoms patients presented were predominantly: fever (100%), multiple lymphadenopathies (90%) and cutaneous rash (25 %) in the presence of serological hyperinflammatory state. These symptoms are frequently predictive factors of MAS (2). According to previous experience (3), in our series, anakinra (at a dosage of 100 mg subcutaneous daily) in association with corticosteroids (pulse steroid or 0.5–1 mg/kg/die of 6-methylprednisolone, followed by oral low dose corticosteroids) represents the first line treatment in 59.5% of patients (25/42 cases). When compared to patients treated with different drugs such as DMARDs, AOSD patients receiving anakinra presented a higher rate of rapid improvement of clinic and normalisation of inflammatory indexes, with sustained remission.

The identification of a hyper-inflammatory state in SARS-nCov-2 infection has legitimated the use of immunosuppressant drugs (4). Born as single-centre experiences, major efforts are concentrated on the use of anti-IL6 therapy (tocilizumab, sarilumab) and JAK inhibitors (baricitinib). Respectively, the evidence of higher levels of IL-6 (an acute phase response protein) in the sera of SARS-nCOV-2 positive patients, and the putative antiviral activity of JAK-inhibitors (potentially involving the mechanism of cellular internalisation of the virus) support the use of these therapeutic strategies. Howevre, benefits and long-term results are still controversial. On the other hand, the few data actually present in the literature about anti-IL1 RA in COVID-19 are limited to a randomised trial comparing anakinra to interferon beta-1A or placebo in patients with an advanced state of disease and in need of ventilatory support, adopting and adapting its use from the previous good results in sepsis (5-9). Based on the similarities of the clinical presentation of COVID-19 and Still's disease, and the safety profile of anakinra demonstrated by our experience in AOSD (well-tolerated and with short half-life), we propose the early use of anti-IL1 RA therapy (anakinra) in the presence of clinical and serological signs of systemic hyper-inflammation state related to COVID-19, at a standard dosage of 100 mg subcutaneously in single administration per day. This therapy in selected cases could be used in association with corticosteroid therapy (but not in the case of non response) and before the failure of non-invasive ventilatory support.

The recognition of the appropriate clinical subset to start anti-IL1RA therapy is mandatory, and rheumatologic experience could be crucial in the multidisciplinary specialistic approach to COVID-19.

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Competing interests: none declared.

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