Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Anakinra in COVID-19: important considerations for clinical trials

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The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 320 000 deaths as of May 19, 2020. COVID-19 deaths are primarily caused by acute respiratory distress syndrome (ARDS) and by a cytokine storm syndrome—ie, a state of hyperinflammation leading to multiorgan failure.[1] A recent *Lancet* letter[2] suggested that screening patients with COVID-19 for hyperinflammation and treating them with immunosuppressive drugs could improve mortality. Cytokine storm complicating macrophage activation syndrome associated with rheumatic disease shares considerable biochemical overlap with the hyperinflammation observed in patients with COVID-19.[1,3]

At the time of writing, there are ten ongoing clinical trials in COVID-19 with the drug anakinra (table). Anakinra inhibits the proinflammatory cytokines interleukin (IL)-1α and IL-1β and has been used with some success to treat macrophage activation syndrome caused by various inflammatory conditions,[4,5] and in several small studies in patients with COVID-19.[6,7] Here we support the rationale for targeting hyperinflammation in COVID-19 with anakinra and comment on different aspects of its use, patient selection, dosing, and outcome measures.

Anakinra is an immunosuppressive drug that carries the theoretical risk of harm in the wrong patient group by potentially targeting beneficial inflammation; however, positive effects might also be missed if the correct patient group is not ascertained. It is important, therefore, to target treatment to individuals considered to have hyperinflammation. Diagnostic criteria in this patient group are poorly developed and there is no consensus, as seen from the inclusion criteria listed for the ongoing anakinra trials (table). Although serum ferritin and IL-6 concentrations are highly specific to hyperinflammation and have been shown to be associated with a need for ventilation in patients with COVID-19,[8] they are not routinely measured in the clinical setting, a shortcoming that is highly relevant given the requirement to identify as many patients as possible that might benefit. We suggest a pragmatic approach to patient selection based on identifying patients with progressive disease and evidence of increasing inflammation. Therefore, we propose using worsening lymphopenia, a marker of disease progression and severity in COVID-19, and increasing C-reactive protein as evidence of worsening inflammation.

The dose and route of administration of anakinra is especially relevant given its short plasma half-life, with both intravenous and subcutaneous routes being considered.[6,7] While a short half-life is beneficial in limiting the drug's duration of action in case of adverse events, it also leads to large peak–trough fluctuations with an intravenous formulation. Variation in dosing needs to be minimised to ensure constant and adequate bioavailability, and to avoid a detrimental rebound

	Population	Intervention	Control	Outcome (primary)	Targeted recruitment (receiving anakinra)	Completion date	Country
NCT04364009 2020-001734-36	Confirmed SARS-CoV-2; patients with respiratory symptoms and requirement of oxygen therapy; CRP >50 mg/L	Intravenous: 200 mg twice a day on days 1–3; 100 mg twice a day on days 4–10	SOC	Treatment success by day 14 (patient alive and not requiring IMV or EMCO)	240 (120)	September, 2020	France
NCT04357366 2020-001466-11	Confirmed SARS-CoV-2; x-ray or CT confirmation of lower respiratory tract infection; plasma soluble urokinase plaminogen activator receptor ≥6 ng/mL	Subcutaneous: 100 mg once a day on days 1–10 and antibiotic (trimethoprim–sulfamethoxazole)	None	Patients not developing serious respiratory failure by day 14	100 (100)	April, 2022	Greece
NCT04324021 2020-001167-93	Confirmed SARS-CoV-2; presence of respiratory distress (PaO_2/FiO_2 <300 mm Hg, or respiratory rate ≥30 breaths per min, or peripheral oxygen saturation <93%); hyperinflammation (lymphocyte counts <1000 cells per μL and two of the following: ferritin >500 ng/mL, LDH >300 U/L, and D-dimer >1000 ng/mL)	Intravenous: 100 mg every 4 h on days 1–15 (comparator group: emapalumab [anti-IFNγ mAb])	SOC	Treatment success by day 15 (proportion of patients not requiring IMV or EMCO)	54 (18)	September, 2020	Italy
NCT04339712 2020-001-039-29	Confirmed SARS-CoV-2; organ dysfunction defined as presence of total SOFA score ≥2 or involvement of lower respiratory tract; macrophage activation syndrome	Intravenous: 200 mg three times a day on days 1–7	SOC	Change of SOFA score; improvement of lung involvement measurements; increased PaO_2/FiO_2 ratio (all by day 8)	40 (20)	April, 2022	Greece
NCT04362111 NA	Confirmed SARS-CoV-2; hyperferritinaemia >700 ng/mL; fever >38°C; any two of the following: increased D-dimers >500 ng/mL or thrombocytopenia <130 000 mm^3, leukopenia (white blood cell count <3500 mm^3) or lymphopenia (<1000 mm^3), elevated AST or ALT >2 times upper limit of normal, elevated LDH >2 times upper limit of normal	Subcutaneous: 100 mg every 4 h on days 1–5	Placebo	No increase in oxygen requirement and no increase in respiratory support measures	20 (10)	December, 2020	USA
NCT04330638 2020-001-500-41	Confirmed COVID-19 diagnosis; PaO_2/FiO_2 <350 mm Hg (on room air) or PaO_2/FiO_2 <280 mm Hg (supplemental oxygen) and requiring high flow or IMV; cytokine release syndrome defined as the following: ferritin >1000 μg/L and rising over last 24 h, or ferritin >2000 μg/L in high flow or IMV patients, or lymphopenia (<800 cells per μL), and two of the following: ferritin >700 μL, increased LDH >300 IU/L, D-dimers >1000 ng/mL, CRP >70 mg/mL; chest x-ray or CT with bilateral infiltrates	Subcutaneous: 100 mg once a day on days 1–28 (comparator groups: with or without siltuximab; with or without tocilizumab)	SOC	2 point improvement on six category ordinal scale or discharge from hospital	342 (171)	December, 2020	Belgium
NCT04341584 2020-001-246-18	Patients in CORIMUNO-19 cohort; CRP >25 mg/L; patients in either group 1: requiring >3 L/min oxygen, WHO progression scale 5, no NIV or high flow; or group 2: respiratory failure and IMV or NIV or high flow, WHO progression scale ≥6, do-not-resuscitate order	Intravenous: 200 mg twice a day on days 1–3; 100 mg twice a day on day 4; 100 mg once a day on day 5	SOC	Survival without need of ventilator use at day 14; WHO progression scale ≤5 by day 4; cumulative incidence of successful tracheal extubation or withdrawal of NIV or high flow at day 14; decrease of at least 1 point in WHO progression scale at day 4	240 (120)	December, 2020	France
NCT02735707 2015-002340-14 (REMAP-CAP)	Suspected or confirmed COVID-19; admission to ICU with symptoms, signs, or both that are consistent with lower respiratory tract infection, and radiological evidence of new onset consolidation; up to 48 h after ICU admission, receiving organ support with one or more of the following: NIV, IMV, vasopressor and ionotropes alone or in combination	Intravenous: 300 mg bolus; 100 mg every 4 h	SOC	All-cause mortality (day 90); days alive and outside of ICU (day 21)	7100 (unspecified)	December, 2023	Global
NCT04366232 2020-001963-10	Confirmed SARS-CoV-2; hypoxic pneumonia (including arterial oxygen saturation <90 mm Hg); CRP >150 mg/L; acute respiratory distress syndrome (including IMV with PaO_2/FiO_2 <300 mm Hg)	Intravenous: 300 mg once a day on day 1–5 (then dose tapering) with or without ruxolitinib	SOC	At least three parameters met (including CRP, ferritin, or both) from: CRP decrease >50%, ferritinaemia decrease >1/3, serum creatine decrease >1/3, AST or ALT decrease >50%, eosinophils >50 mm^3, lymphocytes >1000 mm^3	50 (25)	August, 2020	France
NA 2020-001636-95	Suspected or confirmed COVID-19; receiving organ support with one or more of the following: NIV, IMV, vasopressor and inotropes alone or in combination	Subcutaneous: 100 mg twice a day; or intravenous: 100 mg every 4 h	NA	Plasma IL-1 receptor antagonist and IL-6 on days 1–7	30 (30)	September, 2020	UK

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. CRP=C-reactive protein. SOC=standard of care. IMV=invasive mechanical ventilation. EMCO=extracorporeal membrane oxygenation. NA=not applicable. LDH=lactose dehydrogenase. SOFA=sequential organ failure assessment. AST=aspartate aminotransferase. ALT=alanine aminotransferase. NIV=non-invasive ventilation. ICU=intensive care unit. IL=interleukin.

Table: **Anakinra trials in COVID-19**

increase of inflammation. Pharmacokinetic studies in various disease states have shown that subcutaneous anakinra might ensure adequate and consistent plasma concentrations, with bioavailability ranging from 80–95%.[9,10] Concerns have been raised regarding the suitability of subcutaneous drug administration in patients in intensive care because they are susceptible to the development of peripheral oedema and poor skin perfusion. Repeated subcutaneous injections might also lead to patient discomfort. However, these downsides should be weighed against the considerable benefits of subcutaneous administration in the context of this pandemic, which include easy administration by any health-care professional, increased cost-effectiveness with no need for infusion pumps or equivalent, and reduced fluid load. Reduced fluid load is important as current guidelines for management of severe ARDS recommend a negative fluid balance of 0·5–1·0 L per day,[11] and the most commonly adopted mode of intravenous anakinra results in infusion of a minimum of 400 mL of fluid.

Another important consideration is the choice of how to record the success (or otherwise) of the intervention. It is rare for single trials to provide definitive answers, so a core set of outcomes that are reported by all trials of a given intervention are important to allow systematic reviewers to combine results in similar patient populations.[12] Of the ten identified trials (table), six trials consider patients with a severe condition. These trials are dominated by the REMAP-CAP trial (NCT02735707), which has an open-ended recruitment and a target of 7100 patients. The other five trials have a total of fewer than 400 participants receiving anakinra, with no outcome common to all. Some trials focus on effectiveness (clinical) and others on efficacy (biomarker) endpoints. The other four trials include patients with less severe disease but who are hospitalised, with total recruitment around 250 participants. These trials have a similar mix of effectiveness and efficacy endpoints, with mortality being the most commonly reported outcome. Only five trials explicitly mention ferritin as an outcome, which is regarded as an important parameter for assessing hyperinflammation, and these trials will report data in different ways that will preclude pooling. Even without the clinical heterogeneity inherent in the range of eligibility criteria and dosing regimens under study (table), power for meaningful meta-analysis will be low.

Anakinra is a highly plausible drug candidate in COVID-19, but we encourage trialists to consider patient selection, dosing, and outcome measures, and, importantly, to ensure collection of core outcome measures for current and future trials.

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