Anakinra for severe forms of COVID-19: a cohort study

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Summary

Background **Coronaviruses can induce the production of interleukin (IL)-1β, IL-6, tumour necrosis factor, and other cytokines implicated in autoinflammatory disorders. It has been postulated that anakinra, a recombinant IL-1 receptor antagonist, might help to neutralise the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related hyperinflammatory state, which is considered to be one cause of acute respiratory distress among patients with COVID-19. We aimed to assess the off-label use of anakinra in patients who were admitted to hospital for severe forms of COVID-19 with symptoms indicative of worsening respiratory function.**

Methods **The Ana-COVID study included a prospective cohort from Groupe Hospitalier Paris Saint-Joseph (Paris, France) and a historical control cohort retrospectively selected from the Groupe Hospitalier Paris Saint-Joseph COVID cohort, which began on March 18, 2020. Patients were included in the prospective cohort if they were aged 18 years or older and admitted to Groupe Hospitalier Paris Saint-Joseph with severe COVID-19-related bilateral pneumonia on chest x-ray or lung CT scan. The other inclusion criteria were either laboratory-confirmed SARS-CoV-2 or typical lung infiltrates on a lung CT scan, and either an oxygen saturation of 93% or less under oxygen 6 L/min or more, or aggravation (saturation ≤93% under oxygen 3 L/min) with a loss of 3% of oxygen saturation in ambient air over the previous 24 h. The historical control group of patients had the same inclusion criteria. Patients in the anakinra group were treated with subcutaneous anakinra (100 mg twice a day for 72 h, then 100 mg daily for 7 days) as well as the standard treatments at the institution at the time. Patients in the historical group received standard treatments and supportive care. The main outcome was a composite of either admission to the intensive care unit (ICU) for invasive mechanical ventilation or death.The main analysis was done on an intention-to-treat basis (including all patients in the anakinra group who received at least one injection of anakinra).**

Findings **From March 24 to April 6, 2020, 52 consecutive patients were included in the anakinra group and 44 historical patients were identified in the Groupe Hospitalier Paris Saint-Joseph COVID cohort study. Admission to the ICU for invasive mechanical ventilation or death occurred in 13 (25%) patients in the anakinra group and 32 (73%) patients in the historical group (hazard ratio [HR] 0·22 [95% CI 0·11–0·41; p<0·0001). The treatment effect of anakinra remained significant in the multivariate analysis (HR 0·22 [95% CI 0·10–0·49]; p=0·0002). An increase in liver aminotransferases occurred in seven (13%) patients in the anakinra group and four (9%) patients in the historical group.**

Interpretation **Anakinra reduced both need for invasive mechanical ventilation in the ICU and mortality among patients with severe forms of COVID-19, without serious side-effects. Confirmation of efficacy will require controlled trials.**

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Introduction

The outbreak of COVID-19, due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in Wuhan, Hubei Province, China, and has subsequently spread all over the world. Up to 30% of patients admitted to hospital with COVID-19 need admission to intensive care units (ICUs) to receive ventilation assistance because they develop acute respiratory distress syndrome (ARDS).[1–3] So far, no specific treatment has shown efficacy in preventing worsening of respiratory symptoms in patients admitted to hospital for COVID-19-associated pneumonia requiring oxygen therapy. Finding such a treatment is a public health emergency.

Similarly to other types or coronaviruses (eg, Middle East respiratory syndrome coronavirus), the pathogenesis of SARS-CoV-2 infection includes hyperinflammation that resembles cytokine storm syndromes (eg, secondary haemophagocytic lymphohistiocytosis or macrophage activation syndrome), involving pro-inflammatory interleukins (IL-1β and IL-6) and tumour necrosis factor.[3,4] SARS-CoV-2 is thought to bind to toll-like receptors, which activate the inflammasome and the cleavage of pro-IL-1β by caspase-1, followed by the production of active mature IL-1β, a mediator of fever, lung inflammation, and fibrosis.[5] Coronaviruses encode viroporins, which facilitate viral dissemination through their interaction with cellular ion channels. Additionally, the viroporins E and open reading frame 3a can induce transcription of the gene encoding pro-IL-1β and secretion of IL-1β by activation of the NLRP3 inflammasome.[6,7]

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Research in context

Evidence before this study

With more than 5 103 000 reported cases in the world as of May 23, 2020, the COVID-19 pandemic has become a major cause of acute respiratory distress syndrome and mortality. Analogy with previous outbreaks of other coronaviruses, combined with the accumulating evidence of the pivotal role of the inflammasome pathway in the life-threatening severe acute respiratory distress syndrome coronavirus 2-induced systemic disease, led us to consider interleukin-1 as a target of choice in this particular condition.

Added value of this study

In a cohort of patients with severe forms of COVID-19 who were treated with anakinra, administered subcutaneously at a dose of 100 mg twice daily for 3 days, then 100 mg daily for 7 days, we observed a significant reduction of mortality, along with a significant decrease in the need of mechanical invasive ventilation, with no obvious adverse events, including bacterial infections.

Implications of all the available evidence

Our data suggest that an in-depth evaluation of anakinra in patients with an exacerbating form of COVID-19, mainly resulting from an otherwise uncontrolled cytokine storm, is warranted.

Anakinra is a 17 kD recombinant, non-glycosylated human IL-1 receptor antagonist with a short half-life of about 3–4 h and good safety profile. After the approval of the subcutaneous formulation to treat patients with rheumatoid arthritis, anakinra was found to have some beneficial effects in severe sepsis, but only in the subgroup of patients with multiple organ dysfunction syndrome, in which the inflammasome pathway is also involved.[8] Similar positive results were reported in paediatric patients with secondary haemophagocytic lymphohistiocytosis or macrophage activation syndrome, including cases triggered by viral infection.[8–10]

These data led us to hypothesise that anakinra could represent an efficient treatment for severe forms of COVID-19, predominantly involving the inflammasome pathway. Therefore, we aimed to assess the off-label use of anakinra in patients who were admitted to hospital for severe forms of COVID-19 with symptoms indicative of worsening respiratory function.

Methods

Study design and patients

We did a retrospective cohort study. The Ana-COVID study included a prospective cohort of patients who received anakinra and a historical comparison group who received standard care. Patients were included in the prospective cohort if they were aged older than 18 years and admitted to Groupe Hospitalier Paris Saint-Joseph with severe COVID-19-related bilateral pneumonia; were diagnosed with SARS-CoV-2 infection confirmed by either a positive result from an RT-PCR assay or a typical aspect on CT scan of the lungs (multiple ground-glass abnormalities with crazy paving, absence of lymphadenopathy, and pulmonary nodules); had bilateral lung infiltrates on a lung CT scan or chest x-ray; and had critical pulmonary function defined by oxygen saturation of 93% or less under 6 L/min of oxygen or more or oxygen saturation of less than 93% on 3 L/min with a saturation on ambient air decreasing by 3% in the previous 24 h.

Exclusion criteria were the refusal of the patient to participate, patients who were bedridden and near the end of life, patients with respiratory failure explained by an alternative aetiology, and patients already admitted to the ICU.

The historical comparison group was identified retrospectively from the Groupe Hospitalier Paris Saint-Joseph COVID cohort, which began on March 18, 2020, and included all patients with a COVID-19-related disease. All historical patients had to fulfil the same inclusion and exclusion criteria as those of the anakinra group.

The COVID cohort protocol has been approved by the institutional ethics committee (institutional review board number IRB00012157, initial agreement 401) and registered on the French National Institute of Health Data platform (MR4810020420). All patients were given both oral and written information by their physician about anakinra, and could either accept or refuse this treatment. Their choice was noted in the medical record. All patients in both groups agreed to have their data used for research purposes. This study corresponds to an institutional off-label drug evaluation. In this context, French research regulation (Journal Officiel de la République Française [Official Journal of the French Republic] 0160, July 13, 2018; paragraph 110, MR-004) states that the patient's written consent is not mandatory but investigators are required to give the patient an information leaflet explaining the purpose of the research. The patients' non-opposition to the use of their data for research was also collected in accordance with European regulations (General Data Protection Regulation).

Procedures

Patients in the anakinra group received subcutaneous anakinra (Swedish Orphan Biovitrum, Stockholm, Sweden) at a dose of 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days, in addition to the standard treatment administered at Groupe Hospitalier Paris Saint-Joseph at the time and supportive care. The dose of

anakinra was adapted to renal function and reduced to one daily injection of 100 mg for 72 h, followed by an injection every other day for the next 7 days, in patients under dialysis or with a glomerular filtration rate of less than 30 mL/min.

Patients in the historical group received the standard treatments and supportive care. Standard treatments in Groupe Hospitalier Paris Saint-Joseph at the time included oral hydroxychloroquine 600 mg/day for 10 days, oral azithromycin 250 mg/day for 5 days, and parenteral β-lactam antibiotics (intravenous ceftriaxone 1 g per day or intravenous amoxicillin 3 g per day) for 7 days, in the absence of their respective contraindications. All patients received thromboembolic prophylaxis. No oral corticosteroids or vasopressors were used, but some patients received an intravenous bolus of methylprednisolone (500 mg). Supportive care included low-flow oxygen therapy (≤6 L/min through low-flow nasal cannula) or high-flow oxygen therapy (>6 L/min with high-flow nasal cannula or face mask). None of the patients had invasive or non-invasive mechanical ventilation at baseline.

All data were extracted from our computerised medical record (DxCare [version 12.2.0.1.0], Medasys, Le Plessis-Robinson, France) by two investigators (TH and GD) independently. The data were reported into an electronic case report form that is accessible via an internet browser, using personal accounts. Data were confidentially collected and coded according to the local cohort statements responding to all regulatory points in accordance with French regulations (law 78-17 of Jan 6, 1978, relating to data processing, files, and freedoms) and European General Data Protection Regulation regarding patient information and confidential treatment of all data. The study design and data collection were approved by the institutional review board. All data were monitored by a representative of Groupe Hospitalier Paris Saint-Joseph. The database was frozen for statistical analysis on April 11, 2020. The computerised file used for this research was implemented in accordance with French regulations (law 78-17 of Jan 6, 1978, relating to data processing, files, and freedoms) and European General Data Protection Regulation.

Demographic and medical characteristics, including age, sex, body-mass index (BMI), hypertension, diabetes, cardiopathy, stroke, asthma, emphysema, sleep apnoea, chronic obstructive pulmonary disease, not to be resuscitated status, the severity of the CT lung damage, and the value of the RT-PCR assay at the diagnosis, were recorded from the medical charts. Clinical manifestations, including persistent fever above 38°C, respiratory rate, oxygen saturation, and oxygen therapy requirement, and biological parameters, including neutrophil, lymphocyte, and platelet count, C-reactive protein (CRP), alanine and aspartate aminotransferase, creatinine, lactate dehydrogenase, IL-6, serum ferritin, and D dimer, were recorded at baseline and at discharge from hospital or death.

Not to be resuscitated meant that patient was not eligible for transfer to the ICU. The limitation of care was based mainly on age and comorbidities, along with the opinion of the physician in charge of the patient, with the help of an ad hoc ethics committee.

Chest CT was done with a single inspiratory phase with patients in the supine position. Radiologists classified the CT as typical, equivocal, or negative for COVID-19 and described the main CT features: ground-glass opacity, crazy-paving pattern, and consolidation. A semi-quantitative scoring system was used to estimate the pulmonary involvement of all of these abnormalities on the basis of the area involved: less than 25% (mild involvement); 25–50% (moderate involvement); 51–75% (severe involvement); or more than 75% (diffuse involvement).[11]

Outcomes

The main outcome was the composite of either need for admission to the ICU with invasive mechanical ventilation or death. The other outcomes were death, need for

	Anakinra group (n=52)	Historical group (n=44)	p value
Age, years	71·0 (13·1)	71·1 (14·9)	0·97
Age category	..	..	0·80
<50 years	2 (4%)	1 (2%)	..
50–69 years	23 (44%)	22 (50%)	..
≥70 years	27 (52%)	21 (48%)	..
Sex	..	..	0·21
Male	36 (69%)	25 (57%)	..
Female	16 (31%)	19 (43%)	..
Body-mass index, kg/m²	25·5 (4·0)	29·0 (5·7)	0·0009
Comorbidities	..	..	..
Hypertension	31 (60%)	29 (66%)	0·53
Diabetes	14 (27%)	16 (36%)	0·32
Cardiopathy	9 (17%)	11 (25%)	0·36
Stroke	4 (8%)	7 (16%)	0·21
Pulmonary disease*	8 (15%)	12 (27%)	0·15
Number of comorbidities ≥2 *vs* 0–1	29 (56%)	20 (45%)	0·22
Not to be resuscitated	26 (50%)	20 (45%)	0·66
Positive swab RT-PCR†	36/41 (88%)	33/34 (97%)	0·14
Chest CT	..	..	0·55
Lung infiltrates <50%	31 (60%)	25/38 (66%)‡	..
Lung infiltrates ≥50%	21 (40%)	13/38 (34%)‡	..
Duration of symptoms before inclusion, days	8·4 (4·3)	6·2 (3·6)	0·0088
Clinical inclusion parameters	..	..	0·076
SpO_2 ≤93% under 6 L/min or more oxygen therapy	42 (81%)	41 (93%)	..
SpO_2 ≤93% under 3 L/min oxygen therapy with aggravation§	10 (19%)	3 (7%)	..
Oxygen saturation, %	91·6% (2·4)	92·1% (3·9)	0·53
Oxygen therapy, L/min	7·9 (3·6)	5·6 (3·7)	0·33
Low-flow oxygen therapy	32 (62%)	25 (57%)	0·22
High-flow oxygen therapy	20 (38%)	19 (43%)	..
Persistent fever >38°C	28 (54%)	28 (64%)	0·33

(Table 1 continues on next page)

	Anakinra group (n=52)	Historical group (n=44)	p value
(Continued from previous page)			
Laboratory values	..	..	..
Neutrophil count, ×10⁹ cells per L (normal range 1·8–7·5)	7·48 (5·73)	5·61 (2·89)	0·054
Lymphocyte count, ×10⁹ cells per L (normal range 1–4)	0·84 (0·38)	1·14 (1·12)	0·12
Platelet count, ×10⁹ cells per L (normal range 150–400)	259 (114)	201 (83)	0·0071
C-reactive protein, mg/L (normal <5)	173 (67)	154 (76)	0·20
Lactate dehydrogenase, U/L (normal range 125–220)	514 (216)	428 (190)	0·16
Interleukin-6, pg/L (normal <7)	92·7 (59·5)	..	..
Serum ferritin, µg/L (normal range 30–300)	2025 (2303)	..	..
D dimer, ng/mL (normal <500)	5061 (8689)	2511 (3162)	0·32
Alanine aminotransferase, IU/L (normal <35)	51 (42)	40 (27)	0·18
Aspartate aminotransferase, IU/L (normal <45)	68 (39)	70 (50)	0·79
Creatinine, mg/dL (normal range 0·84–1·21)	1·08 (0·69)	0·99 (0·41)	0·45
Concomitant treatments	..	..	..
Hydroxychloroquine	47 (90%)	27 (61%)	0·0007
Azithromycin	49 (94%)	34 (77%)	0·015
β-lactams	51 (98%)	43 (98%)	0·90
Corticosteroid pulse	2 (4%)	0	0·11

Data are mean (SD) or n (%). *Pulmonary disease included asthma, emphysema, sleep apnoea, and chronic obstructive pulmonary disease. †Swab RT-PCR was not done for 11 patients in the anakinra group and ten patients in the historical group. ‡In the historical group, six patients had a chest x-ray that demonstrated bilateral pneumonia, and no chest CT was done. §Aggravation was defined by a loss of 3% of the oxygen saturation in ambient air over the last 24 h.

Table 1: **Baseline demographic and clinical characteristics**

invasive mechanical ventilation, difference in the mean oxygen therapy requirements between day 0 and day 7, and changes in CRP concentration from day –4 until discharge from hospital or death. In the anakinra group, day 0 corresponds to the date of initiation of anakinra. In the historical group, day 0 corresponds to the first day during which each patient fulfilled the inclusion criteria defined for the anakinra group. Safety outcomes were an increase in liver aminotransferase enzymes (more than three times the upper limit of normal), thromboembolic events (confirmed by a CT pulmonary angiogram for pulmonary embolism and by a venous doppler for deep vein thrombosis of the lower limbs), bacteraemia (confirmed when the patient had a recognised pathogen cultured from one or more blood cultures), and premature discontinuation of treatment.

Statistical analysis

The original total sample size of the prospective cohort study was arbitrarily set at 50 patients in the absence of information on treatment effect. In a classic two-arm trial, with 50 patients per group, there would be 86% power to detect a 50% risk reduction of the primary endpoint, at a two-sided significance level of α=0·05 and assuming a 60% incidence of the primary endpoint.

We did the main efficacy analysis on an intention-to-treat basis (including all patients in the anakinra group who received at least one injection of anakinra). We analysed time-dependent events with a two-sided log-rank test, with the hazard ratio (HR) and two-sided 95% CIs based on a Cox proportional hazards model and the associated Kaplan-Meier survival estimates. We assessed the proportional hazards assumption by testing the interaction between covariates and time. Patients alive were censored on the date of discharge from hospital. We used a multivariate Cox proportional hazards model to take into account effect of covariates on the estimate of treatment effect. Variables were included in the model when they differed statistically between the two groups (p value threshold of <0·05) or when the absolute difference between the two groups (qualitative variables) was greater than 10%.

We compared characteristics of the two groups by use of the χ^2 test or Fisher test when appropriate, for categorical variables and the Student's *t* test for continuous variables. We used a repeated-measures mixed-model testing group effect to analyse CRP concentrations changes over time. A p value of less than 0·05 was deemed to be significant.

We used the SAS (version 9.4) for analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. TH, HB, SJ, ES, GC, and GH had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

From March 24 to April 6, 2020, 52 consecutive patients were included in the anakinra group and 44 historical patients were identified in the Groupe Hospitalier Paris Saint-Joseph COVID cohort study. Clinical, biological, and CT-scan characteristics of the patients in the two groups are compared in table 1. Significant differences between the two cohorts were a lower BMI (mean difference –3·5 kg/m² [95% CI –5·5 to –1·5]; p=0·0009), a longer duration of symptoms before inclusion (2·2 days [0·6 to 3·9]; p=0·0088), a higher platelet count (58×10⁹ cells per L [16 to 99]; p=0·0071), and a higher proportion of patients treated with hydroxychloroquine (29% [12 to 45]; p=0·0007) and azithromycin (17% [3 to 32]; p=0·015) in the anakinra group than in the historical group.

Need for invasive mechanical ventilation or death occurred in 13 (25%) of 52 patients in the anakinra group compared with 32 (73%) of 44 patients in the historical group (HR 0·22 [95% CI 0·11–0·41; p<0·0001; figure 1A). Similar results were observed for death alone (HR 0·30 [95% CI 0·12–0·71; p=0·0063; figure 1B) and need for invasive mechanical ventilation alone (0·22 [0·09–0·56]; p=0·0015; figure 1C).

The treatment effect of anakinra versus historical group on the composite of need for invasive mechanical

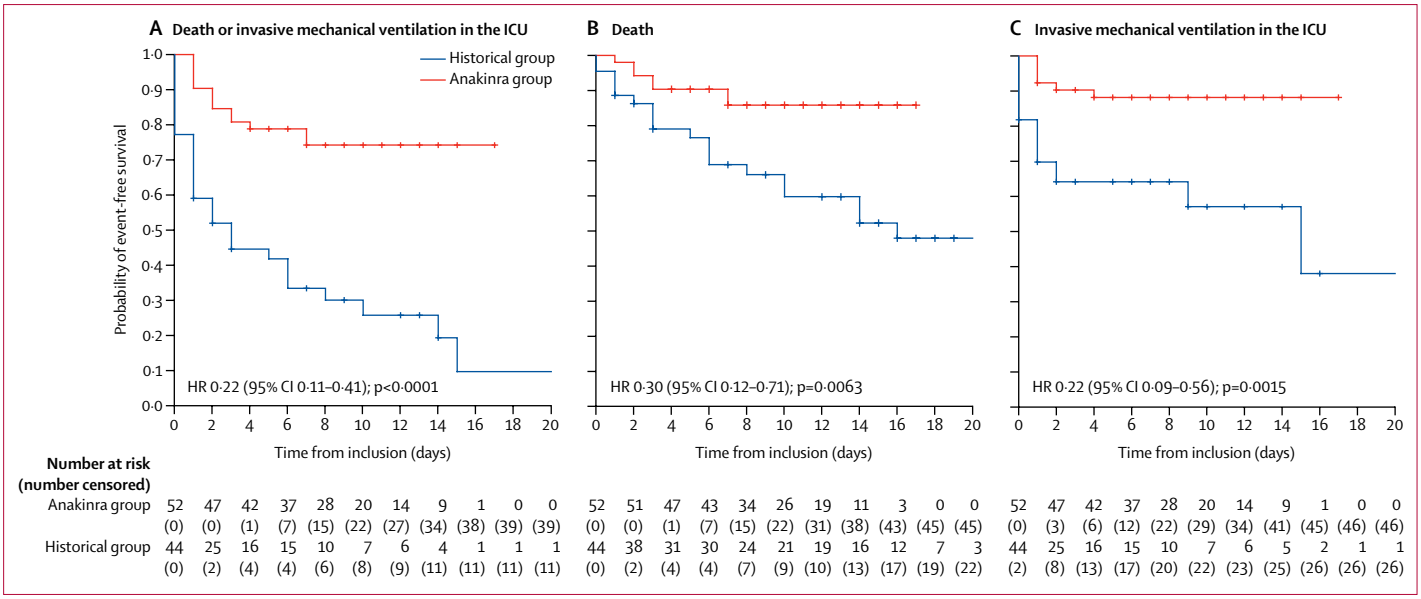

Figure 1: **Kaplan-Meier cumulative estimates of probability of death or invasive mechanical ventilation in the ICU (A), death (B) and invasive mechanical ventilation in the ICU (C) in the anakinra group compared with the historical group**
HR=hazard ratio. ICU=intensive care unit.

ventilation or death remained significant in the multivariate analysis taking into account factors differing at inclusion between the two groups (HR 0·22 [95% CI 0·10–0·49]; p=0·0002; table 2).

Among the 39 patients in the anakinra group who were alive and did not require mechanical ventilation, the mean need for oxygen decreased from a median of 7 L/min (IQR 6–9) at day 0 to a median of 2 L/min (0–4) at day 7 (two missing values). The median difference was –4 L/min (IQR 0–4; p<0·0001, signed-rank test).

From day –4 to day 0, there was a sharp increase in CRP concentration followed by a decrease as early as day 4 of treatment in the anakinra group (figure 2). This result contrasts with the relative stability of CRP concentration over the same time period in the historical group. The difference between the two groups was significant (p<0·0001; interaction test, mixed model). At day 0, 45 (87%) patients in the anakinra group and 36 (82%) patients in the historical group had a CRP concentration higher than 100 mg/L. No patient had a CRP concentration lower than 50 mg/L in both groups.

Seven (13%) patients in the anakinra group and four (9%) patients in the historical group had an increase in liver aminotransferase (more than three times the upper limit of normal). Ten (19%) patients in the anakinra group and five (11%) in the historical group developed a thromboembolic event during the hospital stay. Among the anakinra group, seven (13%) had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis. None of the patients in the anakinra group had a documented bacterial infection during the hospital stay.

	Hazard ratio	95% CI	p value
Anakinra group *vs* historical group	0·22	0·10–0·49	0·0002
Male *vs* female	1·34	0·69–2·62	0·38
Symptom duration >7 days *vs* ≤7 days	1·12	0·51–2·43	0·78
Body-mass index (per kg/m²)	0·99	0·94–1·05	0·75
Number of comorbidities ≥2 *vs* 0–1	0·82	0·41–1·66	0·58
Hydroxychloroquine: treated *vs* untreated	1·35	0·57–3·17	0·50
Azithromycin: treated *vs* untreated	0·82	0·34–1·99	0·66

ICU=intensive care unit.

Table 2: **Estimation of anakinra effect on the composite of invasive mechanical ventilation in the ICU or death, after adjustment for potential confounding factors, using a multivariable Cox proportional hazards model**

Discussion

In this cohort study, anakinra significantly reduced both need for invasive mechanical ventilation in the ICU and mortality among patients with severe COVID-19, without serious side-effects. So far, no specific treatment has been shown to reduce the need for invasive mechanical ventilation and intensive care in patients admitted for COVID-19-associated pneumonia requiring oxygen therapy. A number of ongoing trials are currently testing various pharmacological approaches.[12]

A randomised, controlled, open-label trial of lopinavir–ritonavir in adults with confirmed COVID-19 did not show any beneficial effect in terms of either clinical improvement or mortality.[13] Remdesivir, a new nucleoside analogue prodrug that inhibits RNA polymerase, was administered to 61 patients on a compassionate-use basis, with a clinical improvement seen in 36 (68%) of 53 patients with available data, but a randomised,

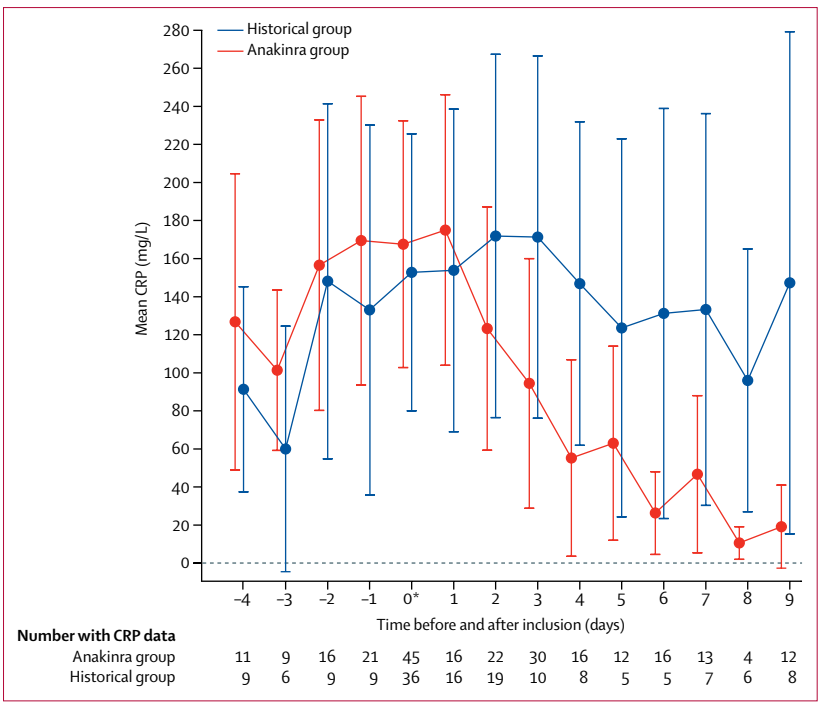

***Figure 2*: Comparison of the mean CRP concentration over time among all patients of the anakinra and historical groups, until discharge from hospital or death**
Error bars indicate SD. CRP=C-reactive protein. *In the anakinra group, day 0 corresponds to the date of initiation of anakinra. In the historical group, day 0 corresponds to the first day during which each patient fulfilled the inclusion criteria defined for the anakinra group.

double-blind, placebo-controlled trial, which included 237 patients, found no clinical benefit of remdesivir versus placebo.[14,15]

The current absence of evidence for antiviral drug efficacy, along with the high mortality associated with severe COVID-19, raises the question of the respective roles of the virus itself and the subsequent occurrence of hyperinflammation, or the so-called cytokine storm. In a study of 150 confirmed COVID-19 cases, predictors of mortality included elevated concentrations of ferritin and IL-6, suggesting a virally driven hyperinflammation,[16] sharing common features with other autoinflammatory disorders, either inherited or acquired (such as adult Still's disease, macrophage activation syndrome, haemophagocytic lymphohistiocytosis, or chimeric antigen receptor [CAR] T-cell-mediated cytokine release syndrome). Furthermore, pulmonary involvement (including ARDS) has been described in secondary haemophagocytic lymphohistiocytosis and in CAR T-cell-mediated cytokine release syndrome.[17,18] Despite the absence of data from randomised controlled trials, the use of the IL-1 inhibitor anakinra seems to be promising in both haemophagocytic lymphohistiocytosis and CAR T-cell-mediated cytokine release syndrome.[9,19–21]

All these data led us to hypothesise that anakinra could represent an efficient treatment for severe forms of COVID-19. Depending on the reported series, the dose of anakinra that was administered in patients with macrophage activation syndrome, haemophagocytic lymphohistiocytosis, or CAR T-cell-mediated cytokine release syndrome varied from 100 mg to 400 mg per day.[9,19,22,23] Concerning a new indication, in a condition in which the persistence of SARS-CoV-2 cannot be ruled out, we decided to select an intermediate dose of anakinra for treating our patients. The dose we chose was irrespective of bodyweight or BMI because the pharmacokinetic profile investigated in healthy individuals of various bodyweights demonstrated modest pharmacokinetic changes.[24] Additionally, given the large therapeutic index of anakinra, we argued that the benefits of fixed dosing (excepting patients under haemodialysis), which reduced the risk of medication error, outweighed the potential reduction in pharmacokinetic variance relative to individuals of heavier bodyweight.

Considering the reduction in both the need for invasive mechanical ventilation and mortality, our study suggests that anakinra might represent an effective treatment for the hyperinflammatory phase of COVID-19. The efficacy of inhibition of IL-1 in patients who received anakinra is reflected by the significant decrease in CRP concentration in the anakinra group, as compared with the historical group (figure 2). The concomitant clinical and biological improvements might provide indirect support for a causal relationship between anakinra treatment and both reduced mortality and admission to ICU for invasive mechanical ventilation.

Notably, a previous Italian study evaluating high-dose intravenous anakinra in patients with severe COVID-19, ARDS, and hyperinflammation also reported significant, comparable benefits for survival and clinical outcomes.[25]

Obviously, both treated and historical groups reported here are not representative of all patients with COVID-19 but correspond to a subpopulation with altered pulmonary function and hyperinflammation, since the majority of our patients had a CRP concentration higher than 100 mg/L. We believe that anakinra should be tested in patients who are admitted to hospital, when clinical and biological parameters are becoming suggestive of a hyperinflammatory status. However, some questions remain, particularly about the optimal situation and time to prescribe this biologic agent, since it is potentially useless in the vast majority of patients with COVID-19, who will only have a benign influenza-like syndrome. A rapid and substantial increase in CRP concentration could represent the best predictor of an evolution from a common viral disease to a systemic and life-threatening disorder.

Assessment of the side-effects of a specific treatment remains difficult in the context of a systemic disease, even more so when a great number of other drugs are prescribed simultaneously to the same patient. In this context, we only noticed an increase in liver aminotransferase levels of more than three times the upper normal limit in seven (13%) patients in the anakinra group and in four (9%) patients in the historical group. The transient increase in liver enzymes is mentioned in the summary of

anakinra characteristics and some cases of reversible drug-induced hepatitis have been reported with this biologic.[26] However, the frequency of elevated liver enzymes in this study was similar between patients who received anakinra and historical controls. Similar findings in an Italian study suggest that it is unlikely that anakinra might be causally linked to such abnormalities in these patients.[25]

The implication of a coagulopathy in patients with COVID-19 strengthens the importance of the detection and management of thromboembolic events.[27] Although such events were not systematically investigated in our study, ten (19%) patients in the anakinra group and five (11%) in the historical group developed such a complication during the hospital stay. Our data did not allow us to determine whether the inhibition of IL-1 was beneficial or detrimental respective to COVID-19-related coagulopathy. Although it has been established that IL-1 increases the level of tissue factor, one of the main activators of coagulation, published data are somewhat contradictory about the effect of blocking IL-1 on coagulability.[28,29]

Our study has several limitations. Taking into account the poor prognosis of COVID-19-related ARDS and the devastating progression of the pandemic, we decided an off-label use of anakinra for all patients with severe forms of the disease. Therefore, the anakinra cohort was compared with an historical group of patients. Consequently, a physician learning curve bias could be hypothesised. However, the recruitment of historical patients in the same institution, during a very short 2-week period is likely to limit this bias. Second, the historical group differed sizeably from the anakinra group for several potentially confounding variables. Obesity was more frequent in the historical group and might have worsened the effects of SARS-CoV-2.[30] In the multivariate analysis of our data, this comorbidity, as well as the other between-group differences, did not affect the estimated effect of anakinra on the outcome. Nevertheless, we cannot rule out the possibility that the observed association could be due, at least in part, to confounding.

In conclusion, in severe forms of COVID-19-related pneumonia requiring oxygen therapy, a 10-day treatment with subcutaneous anakinra was associated with the reduction of both need of mechanical ventilation and mortality, as compared with a historical group with similar characteristics. In the context of this pandemic, with exponential curves of admittances in ICUs, the use of anakinra should be tested more extensively, preferentially through randomised trials, among patients with COVID-19 and symptoms suggesting a virus-induced cytokine storm.

Contributors

TH, J-MN, YB, SL, JE, J-JM, GC, and GH contributed to the study concept and design. TH, OV, SJ, GD, IL, SL, ALB, JLP, SS, JE, and J-JM contributed to patient inclusion. TH, HB, GD, and ES contributed to the acquisition of the datasets. GC did the statistical analysis. All authors developed drafts of the manuscript and approved the final draft.

Declaration of interests

TH reports consultancy fees from Bristol-Myers Squibb. J-JM reports consultancy for Mylan, Pfizer, and Servier. GH reports consultancy fees from Sobi, AbbVie, Bristol-Myers Squibb, Lilly, Novartis, Pfizer, Roche, and Sanofi. All other authors declare no competing interests.

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