Anakinra in the therapy of adult patients with COVID-19

CTS, 23 September 2021

The following information is provided to guide the prescription and to define a relationship between the benefits and risks of the medicine on the individual patient.	
For which patients is it recommended?	In the light of current knowledge, it is believed that the use of anakinra may be permitted only for the treatment of hospitalised adults with moderate/severe COVID-19 pneumonia (with pO_2/FiO_2>150, and not undergoing C-PAP or mechanical ventilation) and with plasma levels of Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR) ≥ 6ng/ml. Co-administration with other interleukin inhibitors or JAK-inhibitors is not permitted.
At what dosages is it preferably prescribed and in what forms?	***Recommended dosage*** The recommended dosage of anakinra in adult patients is 100 mg administered once daily for 10 days by subcutaneous injection. For particular situations, please refer to the technical data sheet of the medicinal product Kineret®.
Who can prescribe the medicine in this emergency phase	Anakinra (Kineret®) is a restricted prescription hospital medicine. For the indication eligible for reimbursement under Law 648/96, the prescription is limited to clinicians working in the centers indicated by the Region for the management of COVID-19.
What are the greatest risks in terms of adverse reactions?	**Warnings** (from data sheet): • Neutropenia and severe infections • Hepatic events For more information on safety, see the technical data sheet of the medicinal product: https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information_it.pdf
Can it be prescribed together with other medicines?	**Main Interactions** (from data sheet)**:** Concomitant treatment of anakinra and TNF-alpha antagonists is not recommended. The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g. IL-1) during chronic inflammation. Therefore, it is possible to predict that for an IL-1 receptor antagonist, such as anakinra, the formation of CYP450 enzymes is normalised during treatment. This event would be clinically significant for CYP450 substrates with a narrow therapeutic index (e.g. warfarin and phenytoin). After the initiation or termination of treatment with Kineret in patients taking these types of medicines, it may be meaningful to consider therapeutic monitoring of the effect or

	concentration of these products and it is possible that the individual dose of the medicine may need to be adjusted. For more information on drug interactions, please see the technical data sheet and consult the website: https://www.covid19-druginteractions.org/.

Classification

Anakinra (Kineret® 100 mg/0.67 mL solution for injection in pre-filled syringe) Anakinra is a human IL-1 receptor antagonist (r-metHuIL-1ra), produced in Escherichia coli cells by recombinant DNA technology, which neutralizes the biological activity of IL-1α and IL-1β by competitive inhibition of their binding to IL-1R1 type I receptors.

Anakinra is indicated for the following clinical conditions:

- Rheumatoid arthritis (RA)
  Kineret is indicated in adults for the treatment of the signs and symptoms of RA in combination with methotrexate with an inadequate response to methotrexate alone.
- Periodic fever syndromes
  Kineret is indicated for the treatment of the following periodic autoinflammatory febrile syndromes in adults, adolescents, children and infants aged ≥ 8 months with a body weight ≥ 10 kg:
- *Cryopyrin Associated Periodic Syndromes (CAPS)*
  Kineret is indicated for the treatment of CAPS, including:
  - Neonatal Onset Multisystem Inflammatory Disease (NOMID) / Chronic, Infantile, Neurological, Skin, Joint Syndrome (CINCA)
  - Muckle-Wells Syndrome (MWS)
  - Familial cold autoinflammatory syndrome (FCAS)
- *Familial Mediterranean fever (FMF)*
  Kineret is indicated for the treatment of familial Mediterranean fever (FMF). If appropriate, Kineret should be administered in combination with colchicine.
- Still's disease
  Kineret is indicated in adults, adolescents, children and infants aged 8 months or above with a body weight of 10 kg or more for the treatment of Still's disease, including systemic juvenile idiopathic arthritis (Systemic Juvenile Idiopathic Arthritis, SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features and moderate to high disease activity, or in patients with persistent disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.

  Kineret can be administered as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs).

  Depending on the different indications, anakinra can be used in various dosages (although the prevalent use is that of 100 mg/day used for RA), while the only mode of administration authorized in CPR is by subcutaneous injection.

In Italy, Kineret is present in the list containing the indications reimbursed by the NHS pursuant to Law 648/96 for the "treatment of patients with auto-inflammatory syndromes in paediatric age - TRAPS (TNFR-Associated Periodic Syndrome) non-responders to first drugs choice" (Italian Official Journal 15/01/2015 no. 11) for the

treatment of "Recurrent cortico-dependent and colchicine-resistant idiopathic pericarditis" (Italian Official Journal 09/01/19 no. 7).

Rationale

Anakinra blocks the physiological receptor and antagonises the state of systemic inflammation generated by the abnormal production of IL-1; the rationale for using this medicine in complex patients with SARS-CoV-2 infection is based precisely on the inhibitory action of the pro-inflammatory stimulation by IL-1.
In fact, SARS-CoV-2 infection induces an excessive and aberrant host immune response, associated with acute respiratory distress syndrome and, in most critically ill patients, a "cytokine storm" (increased plasma and tissue levels of various cytokines that produce long-term damage and fibrosis of lung tissue).
In particular, a hyperinflammatory response, characterised by elevated levels of inflammatory markers (including C-reactive protein, ferritin, interleukin-1 (IL-1) and interleukin-6 (IL-6)) of serum cytokines and chemokines, has been observed in a subgroup of patients with severe COVID-19 *(Jiang et al., 2020; Mehta et al., 2020; Ruan et al., 2020; Hu et al., 2021*). Finally, mounting evidence indicates that this hyperinflammatory response to SARS-CoV-2 contributes to disease severity and death in COVID-19 patients (*Gustine & Jones, 2020*).
In consideration of the role played by IL-1 in the genesis of the inflammatory cascade, it has been hypothesised that therapies that target the cytokines involved in this aberrant inflammatory response (including IL-1) may have an important therapeutic role in delaying the lung damage in patients with SARS-CoV2 infection.
In support of the use of anakinra there is also the evidence in the literature that treatment with anakinra can lead to reductions in mortality and/or the need for invasive mechanical ventilation (*Aouba et al., 2020; Dimopoulos et al., 2020; Filocamo et al., 2020; Franzetti et al., 2020; González-García et al., 2020; Huet et al., 2020; Navarro-Millán et al., 2020; Pontali et al., 2020*). Moreover, high-dose intravenous anakinra has been used off label for the treatment of macrophage activation syndrome and septic shock, conditions that share some clinical and molecular characteristics with COVID-19 hyperinflammation (*Grom et al., 2016; Shakoory et al., 2016*).

Main available evidence

Randomised clinical trials

The main studies and their results are summarised below in chronological order (see also **Annex 1**).

REMAP-CAP (first publication in pre-print form on 25/06/2021)
On 25 June, the final results of the immunomodulatory therapy domain (anti-IL-6, and anti-IL-1) of the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) study, a large open-label, multi-domain, adaptive platform trial to evaluate the efficacy of different treatment options for COVID-19 inpatients, were made available as a pre-print. The immunomodulatory therapy domain enrolled adult ICU inpatients who were randomised to tocilizumab (8mg/kg; n=952), sarilumab (400 mg; n=485), anakinra (300 mg loading dose followed by 100 mg every 6 hours for 14 days; n=373), interferon beta (n=21) or standard non-immunomodulatory therapy (n=418). All but four subjects received respiratory support at enrolment, mainly non-invasive or invasive mechanical ventilation in 42.9% and 32.9% of subjects, respectively. Concomitant steroid therapy was taken in 81.3% of participants and remdesivir in 28.6% of cases.
The median number of days without organ support was 7 (IQR -1, 16), 9 (IQR -1, 17), 0 (IQR -1, 15) and 0 (IQR -1, 15) days for tocilizumab, sarilumab, anakinra and control arm, respectively. The corresponding adjusted

ORs were 1.46 (95%CrI 1.13, 1.87), 1.50 (95%CrI 1.13, 2.00) and 0.99 (95%CrI 0.74, 1.35) for tocilizumab, sarilumab and anakinra, with posterior probabilities of superiority of 99.8%, 99.8% and 46.6%, respectively, compared to control. Considering survival, the adjusted ORs were 1.42 (95%CrI 1.05,1.93), 1.51 (95%CrI 1.06, 2.20) and 0.97 (95%CrI 0.66, 1.40) for tocilizumab, sarilumab and anakinra respectively, compared to control, yielding 98.8%, 98.8% and 43.6% a posteriori probability of superiority over control.
The results of the REMAP-CAP immuno-modulatory domain suggest that, in patients with severe COVID-19 receiving organ support, tocilizumab and sarilumab are equally effective in improving survival and reducing the duration of organ support, while anakinra does not appear to be effective in this specific population of subjects with advanced disease.

SAVE-MORE (first publication in pre-print form on 18/05/2021; full paper *Kyriazopoulou E, et al. Nat Med. 2021 Sep 3. doi: 10.1038/s41591-021-01499-z*)
The SAVE-MORE study (suPAR-guided Anakinra treatment for Validation of the risk and Early Management Of seveRE respiratory failure by COVID-19) is specifically aimed at evaluating COVID-19 patients at risk of progression to severe respiratory failure (IRG) prior to admission to the ICU, by measuring the concentration of soluble urokinase plasminogen activator receptor (suPAR), a plasma biomarker that serves as a prognostic tool for early immune activation and has already been associated with a poor prognosis in several conditions. This is a randomised phase III, double-blind, multicentre study (conducted in Greece and Italy). Adult subjects with a molecular diagnosis of SARS-CoV-2 infection, hospitalised, with pulmonary involvement (but with Pa/FiO2 >150 and not undergoing invasive or non-invasive ventilation) and with suPAR >6 ng/ml were enrolled. Enrolled subjects were randomised (1:2) to receive placebo or anakinra (100 mg/day sc for 7-10 days), in addition to SoC treatment consisting of cortisone (dexamethasone 6 mg/day for 10 days) for severe forms and remdesivir at investigator's discretion (used in 71.9% of participants); other biological drugs were not allowed. The primary endpoint of the study was the frequency distributions of the scores on the WHO 11-point Clinical Progression Scale (CPS) at 28 days. A total of 594 subjects (189 in the placebo arm and 405 in the anakinra arm) were evaluated for the primary efficacy analysis. The mean age of the enrolled population was 62 years, at screening 18.4% of participants (14.3% in the placebo group and 20.2% in the active treatment group) had moderate pneumonia, while 81.6% had severe pneumonia (85.7% in the placebo group and 79.8 in the anakinra group). Other clinical characteristics were evenly distributed between the two study groups. Analysis of the primary endpoint showed an overall improvement in clinical status in subjects treated with anakinra compared to the placebo arm (OR 0.36 worsening of the 11-point WHO-CPS score at 28 days; 95%CI 0.26-0.50). Specifically, 50.4% (204/405) of subjects receiving anakinra were classified as fully recovered without detection of viremia at day 28 compared to 26.5% (50/189) of subjects in the placebo group. A protective effect was also evident in confirmatory analyses required after advice with EMA-ETF: in the group of patients treated with anakinra there were reductions in the number of patients who progressed to severe respiratory failure (IRG) or death (OR 0.46; 95%CI 0.26-0.83), as well as an increase in the number of patients who were discharged from hospital without evidence of COVID-19 infection (OR 0.36, 95%CI 0.25-0.53). The 28-day mortality was also 55% lower among patients in the anakinra arm (3.2%) compared to the SoC alone arm (6.9%). Positive changes in overall improvement and reduction of progression to IRG or death were evident at day 14. Finally, there was a reduction in ICU and hospital length of stay in the anakinra group. In the SAVE-MORE study, the incidence of serious adverse events due to treatment (TEAEs) was lower in patients treated with anakinra and SOC than in patients receiving SOC alone. The incidence of non-serious TEAEs was similar in both treatment groups.

The SAVE-MORE study is the confirmatory study of a small, single-arm, open-label clinical trial (**SAVE** study - suPAR-guided Anakinra treatment for Validation of the risk and Early management of severe respiratory failure by COVID-19, NCT04357366 [Kyriazopoulou E, et al. 2021]), which aimed to evaluate whether early administration of anakinra (100 mg SC QD for 10 days) in subjects with LRTI for SARS-CoV-2 and suPAR >6ng/ml could prevent the development of severe respiratory failure (SRF, defined as a reduction in

pO2/FiO2<150 or need for MV or NIV). A total of 130 subjects treated with anakinra were included, for which an equal number of controls were selected using a propensity-scrore matching technique. 22.3% of subjects (n=29/130) treated with anakinra and 59.2% (n=77/170) of the comparator group progressed to SRF (HR 0.30; 95% CI, 0.20-0.46). The 30-day mortality was 11.5% and 22.3%, respectively (RR 0.49; 95% CI 0.25-0.97). Anakinra was associated with a decrease in circulating interleukin (IL)-6, sCD163 and sIL2-R levels.
The incidence of adverse events (AEs) and serious adverse events (SAEs) detected during the 14-day study period was no higher in the anakinra group than in the comparators, with the only exception of leukopenia which tended to be higher in the anakinra group.

Both studies, SAVE and SAVE-MORE, used a specific marker, soluble urokinase plasminogen activator receptor (suPAR), for the identification of COVID 19 patients at risk of progression to respiratory failure. This would allow anakinra to be used at an early stage, in line with its mechanism of action which, by antagonising the effect of IL-1, would act upstream of the inflammatory signal cascade. The suPAR parameter is already used for prognostic purposes in sepsis (Huang Q et al. 2020). The use of suPAR as a progression marker for COVID-19 is suggested by some literature evidence (Arnold DT et al. 2021; Stauning MA et al. 2021, Oukai et al. 2021; Rovina et al. 2020; Azam et al. 2020) (summarised in Annex 2). In particular, the decision to use a cut-off of 6 ng/ml was derived from a previous study by the Hellenic Sepsis Study Group on a cohort of 57 subjects with COVID-19 pneumonia in which the suPAR level on admission was found to correlate with clinical progression to severe respiratory failure within the first 14 days and, more specifically, a suPAR level ≥ 6 ng/ml was found to be the most appropriate cut-off (sensitivity of 85. 7%, specificity 91.7%, VPP 85.7% and NPV 91.7%).

CORIMUNO-ANA-1 (*Lancet Respir Med 2021*; published online Jan22, 2021)
This is a multicentre, open-label trial with a Bayesan approach, nested within the CORIMUNO-19 cohort.
Subjects with confirmed SARS-CoV-2 infection, COVID-19 pneumonia of mild to moderate severity with a score of 5 on the WHO Clinical Progression Scale (WHO-CPS) who required O2>3L/min supplementation but not in ventilatory assistance, and who had CRP concentrations >25 mg/L were eligible for enrolment in the study (a similar study is in progress, however, conducted on a population with severe COVID-19 - CORIMUNO-ANA-2 - the results of which are not yet available).
Subjects were randomised (1:1) to treatment with anakinra (200 mg BID on days 1-3, 100 mg BID on day 4, 100 mg QD on day 5) in addition to Standard of Care (SoC) or SoC alone.
The two co-primary efficacy endpoints were the proportion of subjects who died or required mechanical ventilation (WHO-CPS>6) at day 4 and the proportion of subjects who survived without the need for mechanical ventilation at day 14.
During the period 8-26 April 2020, 153 subjects were screened. The study was stopped early for futility by the Data and Safety Monitoring Board (DSMB) after recruitment of 116 patients (59 randomised to the anakinra group and 57 to the SoC group).
In the analysable population, the mean age was 66 years (IQR 59 to 76) and 80 (70%) participants were men. At baseline the prevalence of anticoagulant use was 59% in the anakinra group and 53% in the SoC group, that of glucocorticoids was 10% vs 15%, while during the trial the use increased to prevalences of 90% vs 89% and 51% vs 53%, respectively. In the anakinra group, 21/59 (36%) patients had a WHO-CPS score greater than 5 at day 4 compared with 21/55 (38%) in the SoC group (median posterior absolute risk difference [ARD] -2.5%, 90%CI -17.1 to 12.0), with an a posteriori probability of ARD of less than 0 (i.e., anakinra better than SoC) of 61.2%. At day 14, 28 (47%; 95% CI 33 to 59) patients in the anakinra group and 28 (51%; 95% CI 36 to 62) in the SoC group required ventilation or died, with an a posteriori probability of any efficacy of anakinra (hazard ratio [HR] <1) of 54.5% (posterior median HR 0.97; 90% CrI 0.62 to 1.52). At day 90, there was an equal prevalence of deaths (27% in both study groups). Serious adverse events occurred in 27 (46%) patients in the anakinra and 21 (38%) in the usual care group (p=0.45).

ANACONDA Trial (NCT04364009)
This is a randomised, open-label study enrolling subjects with COVID-19 pneumonia on oxygen therapy >4L/min and with FR>24/min or on oxygen therapy even at lower volumes but with rapid worsening and with CRP levels ≥ 50mg/L.

The study was stopped by the Sponsor for efficacy and safety reasons, but the results were never made available (https://clinicaltrials.gov/ct2/show/record/NCT04364009?view=record).

Observational studies

Numerous observational studies, both prospective and retrospective, have evaluated the use of anakinra in subjects with COVID-19.
In particular, a meta-analysis of non-randomised studies conducted by Italian researchers was recently published, in which 4 observational studies were evaluated with a total of 184 subjects included, of whom 111 were treated with anakinra and 73 received SoC treatment (Pasin L et al. 2021). When analysing the data, the authors found significant heterogeneity and the risk of bias was considered high. Overall, treatment with anakinra was associated with reduced mortality (RR 0.26; 95%CI 0.14-0.48) and a lower risk of progression to invasive mechanical ventilation (RR 0.45; 95%CI 0.25-0.82).
The main observational studies (including the two studies conducted in Italy) are reported below.

Huet T et al. 2020
This is a cohort study with historical control conducted in a single French centre (Groupe Hospitalier Paris Saint-Joseph). From 24 March to 6 April 2020, 52 consecutive patients were included in the anakinra group and 44 historical controls were identified. The composite outcome of ICU entry 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 [CI 95% 0.11-0.41; p<0.0001). The effect of anakinra treatment remained significant in multivariate analysis (HR 0.22 [CI 95% 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.

Cavalli G et al. 2020
This is a small single-centre, retrospective cohort study aimed at evaluating the efficacy of off-label administration of high-dose anakinra intravenously, at a dose of 5 mg/kg twice daily, in adult patients with COVID-19 pneumonia with moderate to severe hypoxia and hyperinflammation who were not mechanically ventilated. The results obtained from this group of patients were compared to those of 16 patients receiving standard treatment (200 mg hydroxychloroquine twice daily and lopinavir 400 mg with ritonavir 100 mg twice daily) and to those of 7 patients treated with low doses of anakinra (100 mg twice daily subcutaneously). Subjects with moderate or severe ARDS, PaO2/FiO2 ≤ 200 with positive end-expiratory pressure [PEEP] of at least 5 cm H2O and hyperinflammation (C-reactive protein ≥ 100 mg/L or ferritin ≥ 900 ng/ml) were included in the study. A total of 29 patients (24 men and 4 women, mean age 62 years) with COVID-19, moderate to severe ARDS and hyperinflammation were treated. All patients in the study were receiving non-invasive CPAP (Continuous Positive Airway Pressure) mechanical ventilation and were not in intensive care.
The median duration of treatment was nine days, and treatment was continued until clinical benefit was achieved, i.e. 75% reduction in C-reactive protein and respiratory improvement (defined as PiO2/Fio2 >200) for at least two days, or until death.
After 21 days, 21 (72%) patients treated with high-dose anakinra had improved respiratory function: 13 (45%) patients were discharged from hospital, 3 (10%) no longer required supplemental oxygen, 3 (10%) were

receiving low-flow supplemental oxygen, and 2 (7%) were in the weaning phase from CPAP and no longer had ARDS. Of the 8 patients who did not have improved respiratory function, 5 (17%) were on mechanical ventilation and 3 (10%) died. In the group receiving standard treatment, respiratory improvement was observed in 8 (50%) patients, of whom 7 (44%) were discharged from hospital and 1 (6%) was still admitted and receiving supplemental low-flow oxygen. Of the 8 patients who did not show respiratory improvement, 1 (6%) was on mechanical ventilation and 7 (44%) died. Compared to standard treatment, high-dose anakinra was associated with a higher survival rate at 21 days, with 90% cumulative survival in the anakinra group compared to 56% in the standard treatment group (p=0.009). High-dose anakinra was overall well tolerated in all patients. However, treatment was discontinued due to adverse events in 7 patients (24%) after a median treatment duration of 9 days. In particular, 4 patients (14%) had bacteraemia, while 3 (10%) showed an increase in serum liver enzymes. Treatment discontinuation was not followed by recurrence of systemic inflammation or respiratory dysfunction.

Cavalli G et al. 2021

This is a cohort study conducted in patients with severe COVID-19, respiratory failure and who developed a hyperinflammatory response to the virus, which aimed to evaluate the response to off-label administration of high-dose anakinra, tocilizumab or sarilumab compared to the comparison group treated with hydroxychloroquine, an antiviral and an antibiotic.

Subjects with respiratory failure (PaO2/FiO2 ≤ 300 mm) but not on mechanical ventilation and with hyperinflammation (C-reactive protein ≥ 100 mg/L or ferritin ≥ 900 ng/ml) were included in the study. Between 25 February 2020 and 20 May 2020 at IRCCS Ospedale San Raffaele (MI), 392 patients with COVID-19, respiratory failure and hyperinflammation were enrolled and received the following treatments: 62 patients (16%) received the IL-1 inhibitor anakinra (administered off-label intravenously at a dose of 5 mg/kg twice daily until clinical benefit); 55 patients (14%) received an IL-6 inhibitor (29 patients were given off-label intravenous tocilizumab as a single dose of 400 mg, which was repeated after 24 hours if respiratory function further deteriorated; 26 patients received off-label sarilumab as a single dose of 400 mg intravenously); 275 patients (70%) received standard of care, consisting of hydroxychloroquine and antibiotic and antiviral therapy. The three treatment groups were not well balanced for the main clinical features at baseline. The 28-day survival rate was assessed by the Kaplan-Meier curve and was 68% (CI 95% 61-75) in patients not receiving any interleukin inhibitors, 86% (CI 95% 74-100) in patients treated with IL-1 inhibitors, and 82% (CI 95% 69-97) in patients treated with IL-6 inhibitors. Multivariate analysis showed a significantly reduced risk of mortality in patients treated with anakinra compared to patients who did not receive interleukin inhibitors (hazard ratio 0.450, CI 95% 0.204-0.990, p = 0.047), but not in those treated with IL-6 inhibitors (hazard ratio 0.900, CI 95% 0.412-1.966; p = 0.99). Glucocorticoid treatment was not associated with significant reductions in mortality and adverse clinical outcomes. The benefit of IL-6 inhibitor treatment was most pronounced for increasing serum C-reactive protein concentrations, whereas for decreasing serum lactate dehydrogenase concentrations, patients treated with an IL-1 inhibitor and IL-6 inhibitors had a reduced risk of mortality.

Scientific reviews and meta-analyses

Living systematic reviews and network meta-analyses conducted by leading research groups have become available, summarising the results of clinical trials as they become available.

- In one of the most important living systematic reviews available, carried out by the Cochrane group in collaboration with numerous university and research institutions (https://covid-nma.com/living_data/index.php), the analysis of the available data from RCTs, updated to 15/09/2021, confirms a protective effect of anakinra for the outcome of clinical improvement at 28 days (RR 1. 12; 95%CI 1.03-1.21) and a favourable, although not statistically significant, trend towards a protective effect of anakinra on 28-day mortality outcome (RR 0.69; 95%CI 0.34-1.39) and time to clinical improvement

(RR 1.15; 95% CI 0.91-1.45). However, it should be noted that only two trials were considered in the analysis and that the entire effect was in fact attributable to the SAVE-MORE study.

- 09/08/2021 – *Kyriazopoulou E et al. Lancet Rheumatol 2021*: This is a systematic review and meta-analysis on aggregate and patient-level data. Nine clinical trials (8 observational studies and the randomised trial CORIMUNO-19) were analysed, with a total of 1185 subjects evaluable for aggregate analysis (509 treated with anakinra and 676 controls) and 859 subjects evaluable at patient-level. In the individual patient-level meta-analysis, after adjusting for age, comorbidity, PaO_2/FiO_2 ratio at baseline, C-reactive protein (CRP) concentrations and lymphopenia, mortality was significantly lower in patients treated with anakinra (38 [11%] of 342) compared to those receiving standard care with or without placebo (137 [25%] of 553; adjusted odds ratio [OR] 0.32 [CI 95% 0.20-0.51]). In a subgroup analysis, anakinra was most effective in reducing mortality in patients with higher CRP concentrations >100 mg/L (OR 0.28 [CI 95% 0.17-0.47]). Anakinra also showed a significant survival benefit when administered without dexamethasone (OR 0.23 [CI 95% 0.12-0.43]), but not with dexamethasone co-administration (0.72 [CI 95% 0.37-1.41]). Finally, data from the meta-analysis showed that anakinra was not associated with a significantly increased risk of secondary infections compared with standard of care (OR 1.35 [CI 95% 0.59-3.10]).
- 17/05/2021 – *Barkas F et al. 2021*: This is a meta-analysis that considered 9 studies: 1 prospective study, 6 retrospective studies, 1 randomised open-label trial (CORIMUNO-ANA-1) and 1 open-label trial with propensity-matched comparators (SAVE trial). Aggregate analysis showed a significantly reduced risk of all-cause mortality (OR 0.32; 95% CI 0.23-0.45) and progression to invasive mechanical ventilation (OR 0.38, 95% CI 0.17-0.85) in the anakinra-treated group compared to standard therapy or placebo.

Recommendations by international organisations

- **Anakinra** is not currently included in the main international guidelines (WHO, National Institutes of Health, and Infectious Diseases Society of America).

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