care. This solution presented by the authors during the COVID-19 pandemic has also been reinvented from a corporate and organisational perspective.

Finally, I would suggest that we must rethink the future and recover lost gratitude and self-esteem (as a society and as health professionals), after a pandemic that has been a call for attention and action, to put everything back on track. It is an occasion for examination, learning, and improvement where we can relate to Japanese culture in the concepts of repair (*kintsugi*), reordering (*nankurunaisa*), and harmony (*feng shui*), and take up new challenges in person-centred care.

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Anakinra as a potential alternative in the treatment of severe acute respiratory infection associated with SARS-CoV-2 refractory to tocilizumab: comment☆

Anakinra, una alternativa potencial en el tratamiento de la infección respiratoria grave por SARS-CoV-2 refractaria a tocilizumab: comentario

Dear Editor,

We have read with interest the article by Figuero-Pérez et al. published in the last issue of your journal suggesting the usefulness of anakinra in severe respiratory SARS-CoV-2 infection refractory to tocilizumab[1] and would like to make some observations.

The clinical course of SARS-CoV-2 infection has three distinct clinical phases[2]. In the initial phase there is viral replication with flu-like symptoms and then some patients progress, between day 6 and 13 of symptom onset, to a hyperinflammatory phase with the development of pneumonia that may progress to respiratory distress syndrome.

The pathogenesis of severe SARS-CoV-2 infection involves dysregulation of the immune response with lymphopenia, increased pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-7 or TNF alpha) and a decrease in gamma-interferon. This leads to a systemic inflammatory syndrome with elevated acute phase reactants such as C-reactive protein and ferritin[3].

Treatment of this inflammatory phase with drugs such as dexamethasone or tocilizumab has been shown to reduce mortality[4,5].

Anakinra, an IL-1 receptor antagonist, has recently obtained EMA approval for treatment in adult patients with COVID-19 pneumonia and risk of progression to severe respiratory failure based on the SAVE MORE clinical trial which demonstrated a reduction in 28-day mortality and hospital stay in those treated early with anakinra[6].

There is little evidence regarding rescue therapy in patients with poor clinical outcome despite corticosteroids and/or immunomodulators. In an article published by our group[7], we analysed 143 patients with moderate/severe SARS-CoV-2 pneumonia and hyperinflammation treated with various regimens based on the protocols of that date. We observed that in those who had not responded to corticosteroids with or without tocilizumab, treatment with anakinra could be a useful alternative. Our patients received 100 mg/12 h on day 1 if they weighed between 50 and 60 kg, 100 mg/8 h between 60 and 75 kg or 100 mg/6 h if they weighed >75 kg. Subsequently all received 100 mg/12 h from day 2 to day 6. After adjustment for age and clinical severity indices, anakinra administration was associated with a reduced risk of mortality (HR; .518, 95% CI .265–.910, $p = .0437$).

In the case published by Figuero-Pérez et al.[1] we consider that it cannot be suggested that the patient's clinical improvement was due to anakinra when a single dose of 100 mg was administered. Given that the half-life of anakinra is 4–6 h and that of tocilizumab around 6 days, it is likely that the patient's improvement was due to the effect of tocilizumab. There is currently no consensus on the optimal doses of anakinra in this clinical setting, but higher and longer doses have been used in the literature[8,9].

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Use of anakinra in the treatment of SARS-CoV-2 severe respiratory infection☆

Uso de anakinra en el tratamiento de la infección respiratoria grave por SARS-CoV-2

Dear Editor,

We would first like to thank Aomar-Millán et al.[1] for their response to our article in which we suggested the potential benefit of anakinra in the treatment of SARS-CoV-2 infection refractory to tocilizumab treatment.[2]

The "cytokine storm" secondary to SARS-CoV-2 infection leads to severe COVID-19 disease. Excessive activation of the immune system produces a picture like that of HLH.[3] Increased levels of proinflammatory cytokines (IL-1, IL-6, or TNF-alpha), procoagulant factors and lymphopenia play a major role in its pathogenesis.

The use of immunosuppressants such as dexamethasone and anti-IL-6 (tocilizumab) and anti-IL-1 (anakinra) antibodies are the mainstay of treatment of the inflammatory phase of SARS-CoV-2 infection.[4]

As reported by Aomar-Millán et al., anakinra has recently been approved by the EMA for the treatment of patients with SARS-CoV-2 pneumonia who require supplemental oxygen therapy and who are at risk of progressing to severe respiratory failure as determined by a plasma concentration of soluble urokinase-type plasminogen activator receptor (suPAR) ≥6 ng/mL. This approval was based on the SAVE MORE study,[5] which demonstrated a decrease in mortality and hospital stay in patients treated early with anakinra.

Interestingly, the retrospective study by Aomar-Millán et al.[6] analysed 143 patients with SARS-CoV-2 pneumonia. Patients refractory to treatment with corticosteroids and tocilizumab were treated with anakinra at a dose of 100 mg/every 8–12 h between day 2 and 6. Administration of anakinra was associated with a reduced risk of mortality (HR: .518; 95% CI: .265 – .910; p = .0437).

The patient described in our article[2] received 2 doses of tocilizumab (8 mg/kg, subcutaneously) and, given the absence of respiratory and analytical improvement 48 h after tocilizumab administration, it was decided to administer anakinra (100 mg single total dose, subcutaneously). At the time the patient was admitted to hospital (April 2020), the use of anakinra in the inflammatory phase of SARS-CoV-2 pneumonia was under study. Therefore, no recommended dose had been described in the literature at that time. Currently, although there is still no consensus, higher doses and several days of continuous treatment are recommended.[5–7] Like Aomar-Millán et al. in their response, we considered in the discussion of our article that the clinical improvement of the patient could not be explained solely by the effect of treatment with anakinra, and that a late benefit of tocilizumab should not be ruled out.

Conflict of interests

JJC-H: Consulting or Advisory Role: MSD Oncology, Bristol-Myers Squibb, Merck Speakers' Bureau: MSD Oncology, Bristol-Myers Squibb, Merck, Roche, Janssen Oncology, AstraZeneca Travel, Accommodations, Expenses: MSD Oncology; the remaining authors have no conflict of interests to declare.

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