



Anakinra for the prophylaxis of venous thromboembolism in patients with COVID-19

Chia Siang Kow¹ · Dinesh Sangarran Ramachandram² · Syed Shahzad Hasan^{3,4}

Received: 9 March 2023 / Accepted: 22 March 2023 / Published online: 10 April 2023
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2023

Keywords VTE · anticoagulant · interleukin-1 · neutrophils · neutrophils

Bektaş et al. (2023), in a retrospective observational study, investigated the effect of high-dose intravenous anakinra on the clinical outcomes in patients with severe and critically ill coronavirus disease 2019 (COVID-19), compared to the standard of care. Expectedly, after propensity score matching of two groups of participants, the use of high-dose intravenous anakinra was associated with reduced admission into the intensive care unit (14.1% versus 30.8%) and reduced mortality (14.1% versus 32.1%), compared to standard of care. Furthermore, the reduced mortality with high-dose intravenous anakinra compared with standard of care was also apparent after adjustment of covariates in the multivariate analysis.

The findings of clinical benefits concur with those reported in the randomized controlled trial (Kyriazopoulou et al. 2021) of intravenous anakinra in patients with COVID-19. To illustrate, in the SAVE-MORE, double-blind, randomized controlled trial, intravenous anakinra treatment guided by soluble urokinase plasminogen receptor plasma levels resulted in more than 50% of the relative decrease in the 28-day mortality (hazard ratio = 0.45; 95% confidence interval 0.21–0.98; $P = 0.045$), compared to placebo (Nguyen et al. 2023).

In addition to the mortality benefits, we are particularly interested in the findings that high-dose intravenous

anakinra was associated with reduced occurrence of pulmonary embolism (4.1% versus 9.0%), compared to standard of care (Bektaş et al. 2023). Although the difference did not achieve statistical significance, probably due to the low number of participants, we believe it is of clinical importance to explore further the potential for high-dose intravenous anakinra to reduce the risk of venous thromboembolism in patients hospitalized with COVID-19.

The ability of anakinra to reduce the occurrence of venous thromboembolism is not without its pharmacological plausibility. Growing understanding of the pathophysiology of COVID-19-related thrombosis has led to our findings that NETosis act as a scaffold for thrombus formation in patients with COVID-19 (Kow et al. 2020). As a recombinant interleukin-1-beta (IL-1 β) receptor antagonist, anakinra prevents the binding of the proinflammatory cytokines IL-1 β to the IL-1-receptor type 1, thus inhibiting the downstream IL-1 β signaling. Previously, it has been shown in vitro that IL-1 β -induced ceramide synthesis could trigger neutrophil extracellular trap formation (NETosis). Interestingly, IL-1 β -induced NETosis can be attenuated in vitro by anakinra which interferes with IL-1 β signaling (Meher et al. 2018).

Therefore, we believe the findings where high-dose intravenous anakinra resulted in reduced occurrence of pulmonary embolism, as reported by Bektaş et al. (2023), may not be entirely a coincidence. Although the reduced risk of venous thromboembolism was not apparent in the SAVE-MORE trial (Kyriazopoulou et al. 2021), the dose of anakinra treatment in the trial (100 mg daily) may be too low to elicit its clinical benefits on reduced venous thromboembolism. Indeed, the dose of anakinra administered in the retrospective observational study by Bektaş et al. (2023) was 400 mg daily with gradual up-titration to a maximum dose of 1,600 mg daily (10 mg/kg/day), if necessary. Future clinical trials investigating anakinra in patients with COVID-19

✉ Chia Siang Kow
chiasiang_93@hotmail.com

¹ School of Pharmacy, International Medical University, 126, Jalan Jalil Perkasa, Bukit Jalil, Kuala Lumpur, Malaysia

² School of Pharmacy, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia

³ School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom

⁴ School of Biomedical Sciences & Pharmacy, University of Newcastle, Callaghan, Australia

should administer a high-dose regimen to determine their efficacy on risk reduction of venous thromboembolism. Anakinra may be a safer alternative to anticoagulant therapy for preventing venous thromboembolism in patients with COVID-19 without associated bleeding risk.

Acknowledgements N/A.

Funding The preparation of this article did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Conflict of interest All authors declare no conflicts of interest.

References

Bektaş M, Yüce S, Ay M, Uyar MH, Önder ME, Kılıç Mİ (2023) High-dose intravenous anakinra treatment is safe and effective in severe and critical COVID-19 patients: a propensity score-matched study in a single center [published online ahead of print, 2023 Jan 27]. *Inflammopharmacology* 1–11.

Kow CS, Hasan SS (2021) Colchicine as an adjunct to heparin for prophylaxis of venous thromboembolism in patients with COVID-19. *Rheumatol Int* 41(3):677–678

Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, Fragkou A, Rapti A, Damoulari C, Fantoni M, Kalomenidis I, Chrysos G, Angheben A, Kainis I, Alexiou Z, Castelli F, Serino FS, Tsilika M, Bakakos P, Nicastrì E, Tzavara V, Kostis E, Dagna L, Koufargyris P, Dimakou K, Savvanis S, Tzatzagou G, Chini M, Cavalli G, Bassetti M, Katrini K, Kotsis V, Tsoukalas G, Selmi C, Bliziotis I, Samarkos M, Doumas M, Ktena S, Masgala A, Papanikolaou I, Kosmidou M, Myrodi DM, Argyraki A, Cardellino CS, Koliakou K, Katsigianni EI, Rapti V, Giannitsioti E, Cingolani A, Micha S, Akinosoglou K, Liatsis-Douvitsas O, Symbardi S, Gatselis N, Mouktaroudi M, Ippolito G, Florou E, Kotsaki A, Netea MG, Eugen-Olsen J, Kyrianiou M, Panagopoulos P, Dalekos GN, Giamarellos-Bourboulis EJ (2021) Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med* 27(10):1752–1760

Meher AK, Spinosa M, Davis JP, Pope N, Laubach VE, Su G, Serbulea V, Leitinger N, Ailawadi G, Upchurch GR Jr (2018) Novel role of IL (Interleukin)-1 β in neutrophil extracellular trap formation and abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol* 38(4):843–853

Nguyen T, Dima L, Willett KC (2023) Anakinra-An Interleukin-1 Receptor Antagonist for COVID-19 [published online ahead of print, 2023 Feb 22]. *Am J Ther* <https://doi.org/10.1097/MJT.0000000000001603>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.