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.

COVID-19 cytokine storm: targeting the appropriate cytokine

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Published Online
February 3, 2021
https://doi.org/10.1016/
S2665-9913(21)00011-4

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As of January, 2021, nearly 2-million deaths worldwide have been attributed to COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Much of the mortality has been associated with a cytokine storm syndrome in patients admitted to hospital with COVID-19 pneumonia.[1] Defining the COVID-19 cytokine storm syndrome has been challenging, but early reports proposed combinations of clinical (eg, fever) and laboratory (eg, hyperferritinaemia) features in determining patients most likely to benefit from cytokine storm syndrome treatment.[2,3] A vast array of anti-inflammatory therapies are being explored to dampen the cytokine storm syndrome to save lives. One of the first approaches to treat COVID-19 cytokine storm syndrome was targeting interleukin-6 (IL-6). Early during the pandemic, IL-6 concentrations were noted to be elevated, and IL-6-blocking therapies were available in China, whereas IL-1 inhibitors were not. Retrospective case series of monoclonal antibodies binding IL-6 or its receptor presented mixed results in potential benefit in treating COVID-19 cytokine storm syndrome; however, most randomised controlled trials have not documented improved survival with agents targeting IL-6.[4] By contrast, targeting IL-1, another pro-inflammatory cytokine that has been targeted effectively in other cytokine storm syndromes,[5] has been reported to be largely successful in improving COVID-19 survival based on retrospective cohort studies.[6]

In *The Lancet Rheumatology*, Giulio Cavalli and colleagues compared the effectiveness of IL-1 and IL-6 inhibition in the treatment of COVID-19 cytokine storm syndrome.[7] This single-centre, observational study of patients admitted to hospital with COVID-19, respiratory insufficiency, and hyperinflammation (elevated C-reactive protein ≥100 mg/L or ferritin ≥900 ng/mL) analysed mortality in those receiving an IL-1 receptor antagonist (anakinra; n=62) or one of two monoclonal antibodies binding the IL-6 receptor (tocilizumab or sarilumab; n=55) versus no interleukin inhibition (n=275). The study suffers from potential biases that are frequent in non-randomised studies, but the authors controlled for baseline clinical differences among groups using multivariable Cox regression analysis, as well as immortal bias by excluding early (within 24 h from enrolment) deaths and intensive care admissions. Moreover, many in the no interleukin inhibition group were offered one of the anti-cytokine interventions but chose not to receive them. As this cohort occurred before the reports of glucocorticoid benefits,[8] very few patient outcomes were confounded by glucocorticoid therapy. With these caveats in mind, the 28-day survival (primary outcome) was 68% (95% CI 61–75) in the no interleukin inhibition population, 86% (74–100) for the patients who received the IL-1 inhibitor (lower mortality risk with a hazard ratio [HR] of 0·450, 95% CI 0·204–0·990; p=0·047), and 82% (69–97) for patients who received IL-6 inhibitors (0·900, 0·412–1·966; p=0·79). However, interaction tests revealed a lower mortality risk in the IL-6 inhibition group in those with increasing serum C-reactive protein concentrations. In addition, there was no evidence of adverse clinical outcome (a composite of death or mechanical ventilation) for either of the anti-cytokine treated groups compared with no interleukin inhibition. Thus, the recombinant human IL-1 receptor antagonist, anakinra, which blocks signalling of both IL-1α and IL-1β, significantly improved COVID-19 survival.

Comparative effectiveness studies are uncommon trial designs for prospective randomised trials, particularly in the setting of a pandemic. Cohort studies, if properly analysed for various potential biases, can shed light on comparing possibly equivalent therapies (equipoise) for various conditions. Observational studies often suffer from lack of uniformity in treatment, but do allow for physician thoughtfulness and individualisation of care. For example, in this report, anakinra, which has a short half-life (about 4 h) was given at a high dose (10 mg/kg per day divided twice daily) and was not tapered until clinic benefit (defined respiratory and laboratory parameters) was achieved.[7] This regimen differs substantially from that used in many randomised trials, which might use this treatment for 3–5 days at lower doses and then stop treatment irrespective of outcome. Why IL-1 blockade is proving more beneficial than IL-6 inhibition is unclear but might be related to the endotheliopathy associated with COVID-19 and the release of IL-1α, or the fact that IL-1 is frequently upstream of IL-6 expression, so blocking IL-1 signalling also indirectly blocks IL-6.[9] Subsets of patients with COVID-19 might benefit from IL-6 blocking therapeutics, particularly early during the cytokine storm syndrome, as has been seen for IL-1 inhibition

of cytokine storm syndrome.[5] However, such subsets have yet to be identified and might include those with low lactate dehydrogenase concentrations.[7] Ultimately, a personalised medicine approach to treating various cytokine storm syndromes, COVID-19 and others, should result in improved survival. Trial design will be crucial, both in terms of selecting patients most likely to benefit (stricter criteria for cytokine storm syndrome) from cytokine-targeted treatments of COVID-19, as well as therapeutics approaches (eg, longer duration of treatment and combination treatment, such as cytokine blockade plus glucocorticoids, as seen in other cytokine storm syndromes[10]). From the report of Cavalli and colleagues,[7] and others, anakinra appears to be promising for saving the lives of patients with COVID-19 cytokine storm syndrome, and we all anxiously await prospective randomised controlled trails to confirm this optimism.

I report grants and personal fees from Sobi, Novartis, and Pfizer during the conduct of the study.

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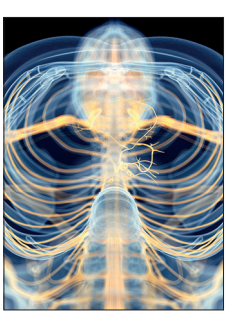
Hacking the inflammatory reflex

Medical breakthroughs create surprises. But medicine abhors surprise, so breakthroughs often begin life being viewed as alternative treatments or being scorned as quack ideas. Consider, for example, Ignaz Semmelweis, who in 1847 discovered that handwashing improved survival of women with peripartum infection, especially when gloveless medical students doing autopsies washed their hands before delivering babies. Despite rigorous statistical proof, Ignaz's breakthrough ideas infuriated his colleagues, who committed him to an asylum, where he died at age 47 years at the hands of his prison guards. Decades later, Louis Pasteur provided the scientific mechanism explaining Ignaz's findings and picked up the cause of advocating for physician handwashing. He too faced the wrath and scorn of physicians who derided and ridiculed the germ theory as quackery. Clearly medical breakthroughs are often more evolutionary than revolutionary.[1,2]

In *The Lancet Rheumatology*, Sara Marsal and colleagues report the results of a new study based on the breakthrough idea to use electronic devices, not drugs, as a treatment for rheumatoid arthritis.[3] This prospective, multicentre, uncontrolled, open-label study included patients with moderately to severely active rheumatoid arthritis and insufficient response to previous treatment with conventional synthetic or biological disease-modifying antirheumatic drugs. Therapy comprised daily stimulation (up to 30 minutes per day) of the sensory branch of the vagus nerve innervating the ear using a wearable battery-operated electronic device that delivered 20 kHz pulses. The authors observed highly significant mean changes in Disease Activity Score of 28 joints with C-reactive protein (DAS28-CRP) at 12 weeks (mean change −1·4 [95% CI −1·9 to −0·9]; p<0·0001), and American College of Rheumatology (ACR) responses of 16 (53%) of 30 patients for ACR20, 10 (33%) for ACR50, and five (17%) for ACR70. Ultrasound and MRI imagining revealed significant improvement in synovitis, tenosynovitis, osteitis, and bone erosion scores. The authors conclude that this alternative treatment should be evaluated in larger controlled studies for rheumatoid arthritis. So does "alternative" in this case mean quackery or breakthrough? And what is the scientific mechanism behind these findings?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Published **Online**
February 1, 2021
https://doi.org/10.1016/S2665-9913(20)30448-3

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