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Published Online  
October 15, 2020  
[https://doi.org/10.1016/S2665-9913\(20\)30361-1](https://doi.org/10.1016/S2665-9913(20)30361-1)

See Online for appendix

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## The Lazarus effect of very high-dose intravenous anakinra in severe non-familial CNS-HLH

The interleukin (IL)-1 receptor antagonist, anakinra, is recognised to be effective in secondary haemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS).<sup>1</sup> Mostly used subcutaneously, intravenous anakinra has been described for the cytokine storm characteristic of secondary HLH or MAS and variably for neurological involvement in HLH, but not specifically for refractory CNS-HLH<sup>2</sup> (appendix p 5). Here, we describe a child with life-threatening secondary HLH on high-dose intravenous anakinra infusion, whose disease course was complicated by CNS-HLH that responded to a steep escalation of the anakinra dose.

The patient (female, white, aged 9 years) presented with 3 weeks of high fevers, severe abdominal and leg pains, with normal appendix on appendectomy. On arrival at our tertiary centre, she rapidly collapsed with protracted cardiovascular instability necessitating inotrope, pressor, and inodilator support; ventilation; haemofiltration for severe renal failure; and multiple transfusions for severe coagulopathy. Concurrent laboratory results showed severe HLH (appendix pp 1–2). She received pulsed intravenous methylprednisolone at 30 mg/kg per day for 3 days (followed by 2 mg/kg per day of prednisolone equivalent); intravenous immunoglobulin (2 g/kg in divided doses); and empiric antimicrobials (intravenous acyclovir and intravenous ceftriaxone). She was switched to meropenem and teicoplanin on deterioration. Given her rapidly progressive multiorgan

dysfunction, hypoperfusion, and subcutaneous oedema, high-dose intravenous anakinra infusion was commenced at 12 mg/kg per day, after a loading dose.

Despite an initial response, HLH parameters plateaued with neurological deterioration, wherein she developed fixed dilated pupils and clonus, with cerebral function monitoring equivalent to a flat EEG, despite minimal sedation for ventilation. She was too unstable for an MRI scan. CT of the head revealed no focal pathology or posterior reversible encephalopathy syndrome. Given clinical evidence of CNS-HLH, intravenous methylprednisolone was substituted with high-dose dexamethasone, with no neurological improvement. Clinical instability with profuse bleeding precluded CSF testing and intrathecal therapy. She was moribund with generalised oedema and bleeding from procedural sites. Due to features suggesting extensive irreversible brain injury, withdrawal of ventilation was discussed with family, because further imminently effective therapeutic options appeared unviable.

However, based on favourable evidence in adults with subarachnoid haemorrhage,<sup>3</sup> intravenous anakinra was increased to 2 mg/kg per h (48 mg/kg per day) for 3 days. Within 36 h of dose escalation, clear signs of neurological recovery were evident, followed by sustained improvement. A single dose of renal-adjusted, low-dose etoposide was administered. Anakinra infusion was weaned over 2 weeks and converted to subcutaneous dosing once stable (appendix p 4). Ciclosporin was commenced when renal dysfunction resolved. Subsequent MRI of the head revealed mild global brain volume loss, consistent with prolonged paediatric intensive care unit admission, but no other pathology. Intercurrent infections were appropriately treated. Apart from sustaining a residual post-ischaemic necrotic patch (appendix p 3) and transient alopecia, she recovered with no cognitive dysfunction. She was

discharged after 8 weeks, on anakinra, steroids, ciclosporin, and fluconazole prophylaxis, all therapy was eventually stopped successfully. Investigations for primary or genetic HLH were negative (appendix pp 1–2), the exact trigger remains unknown.

Severity of neurological involvement in secondary HLH varies significantly, often heralds poor prognosis, and treatment of refractory CNS-HLH is challenging.<sup>4</sup> Because of a paucity of clinical trials, recommended management includes steroids (dexamethasone), immunosuppression (eg, etoposide or ciclosporin) and intrathecal therapy (eg, methotrexate or steroids). Unless HLH is Epstein-Barr virus-driven, wherein rituximab might be beneficial, additional therapy (including alemtuzumab, anti-thymocyte globulin, ruxolitinib, interferon gamma blockers or salvage experimental therapy) is costly, difficult to procure in an emergency setting, experimental, or fraught with side-effects. Haematopoietic stem cell transplantation is described in familial HLH, CNS-familial HLH, and isolated CNS-HLH. In patients with rapidly deteriorating multiorgan dysfunction requiring time-critical intervention, these therapies might not be readily accessible or practicable.

Previously, anakinra has been reported to be effective in febrile infection-related epilepsy syndrome,<sup>5</sup> a non-HLH-related refractory epileptic encephalopathy in children, administered 5 mg/kg twice daily subcutaneously. Our patient was already on 12 mg/kg per day intravenous anakinra when she became unresponsive.

Studies in adults with subarachnoid haemorrhage have explored the role of IL-1 inhibition in mitigating effects of neuroinflammation. After a pilot study of intravenous anakinra (2 mg/kg per h) in subarachnoid haemorrhage, which showed that it was safe, penetrated the blood-brain barrier, and achieved experimentally therapeutic concentrations, a dose-ranging study

showed significant demonstrable CSF penetration (1.6% relative to plasma concentration) with proposed neuroprotection.<sup>3</sup> Subsequently, anakinra has been proposed as a promising therapeutic option for preventing inflammation and delayed cerebral ischaemia in subarachnoid haemorrhage patients.

We used this rationale of very high-dose intravenous anakinra infusion being safe and able to cross the blood-brain barrier, conferring possible neuroprotection within a therapeutic time window, to successfully treat our patient. Because she was already on high-dose anakinra (12 mg/kg per day), due to ongoing CNS-HLH, we extrapolated available evidence in subarachnoid haemorrhage<sup>3</sup> and sepsis<sup>2</sup> patients, and escalated anakinra infusion to 2 mg/kg per h (48 mg/kg per day) for 72 h, subsequently tapered. With this regimen, our patient effectively showed neurological reversal and eventually recovered without deficits, despite extreme neurological obtundation. The anakinra dose in our patient was escalated from an already high dose infusion to achieve this neurotherapeutic effect successfully. Almost 3 years on, she remains well and neurologically normal.

Furthermore, we administered anakinra despite intercurrent infections (which resonates with the high safety profile observed in previous studies)<sup>2</sup> and therapeutic doses despite renal failure, while on haemofiltration.

In the context of the COVID-19 pandemic, neurological associations of COVID-19 are increasingly described, however, encephalopathy secondary to severe HLH (akin to CNS-HLH) has not been characterised, where awareness of alternative therapeutic options might be beneficial.

In summary, we report very high-dose intravenous anakinra for successful treatment of non-familial CNS-HLH. This might be a potential therapeutic option and possibly neuroprotective if used promptly, rationally and appropriately, while awaiting

prospective controlled studies in this subset of patients.

We are grateful to John Reynolds, Chair of Medicines Management and Therapeutics Committee, Oxford University Hospitals NHS Foundation Trust (Oxford, UK) for timely approval of high-dose anakinra therapy. We gratefully acknowledge Kimberly Gilmour, Consultant Clinical scientist, Great Ormond Street Hospital (London, UK) for interpreting the HLH genetics results. DK acknowledges the NIHR Oxford Biomedical Research Centre (Oxford, UK) for funding his salary as consultant in paediatrics and vaccinology. No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this Correspondence. AK reports personal fees from one-off honorarium from Novartis for a Still's disease Advisory Board meeting for standard of care and patient pathway in the UK (October, 2019), Educational meeting-support grant (no personal fees or travel allowance) via Sobi as member of SAID-UK (Systemic AutoInflammatory Diseases network-UK), outside the submitted work; all other authors declare no competing interests. JEGC reviewed the case history, and drafted and revised the Correspondence. AK devised the study, was involved in patient management, provided early draft revisions, and critical review of the Correspondence. SS, DK, SW, AQ, EB, JW, DO'S, and KB were involved in patient management, provided critical review of the Correspondence and subspecialty input. AK and JEGC contributed equally. Written consent for publication was obtained from the patient's legal guardian.

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## Serious infection with tofacitinib in patients with rheumatoid arthritis: the importance of context

Published Online  
September 16, 2020  
[https://doi.org/10.1016/S2665-9913\(20\)30211-3](https://doi.org/10.1016/S2665-9913(20)30211-3)

Published Online  
September 17, 2020  
[https://doi.org/10.1016/S2665-9913\(20\)30334-9](https://doi.org/10.1016/S2665-9913(20)30334-9)

We read with interest Ajinkya Pawar and colleagues' Article on the risk of hospital admission for serious infection in patients with rheumatoid arthritis after initiating either tofacitinib or biologic disease-modifying anti-rheumatic drugs (bDMARDs),<sup>1</sup> and Ennio Giulio Favalli's accompanying Comment.<sup>2</sup> Pawar and colleagues compare tofacitinib with seven bDMARDs in 130 718 patients with rheumatoid arthritis across three US medical insurance databases.<sup>1</sup> We noted several misleading statements that we believe do not reflect all the data and warrant your readers' attention.

Pawar and colleagues state in their summary that their study "found potential differences between tofacitinib and several bDMARDs in the risk of admission to hospital for serious infection".<sup>1</sup> However, significant differences were seen only for tofacitinib versus etanercept. When tofacitinib was compared with other bDMARDs, the incidence of serious infection was similar (adalimumab and certolizumab) or differed numerically but not significantly (abatacept, golimumab, tocilizumab, and infliximab). With the exception of infliximab, the observed differences each favoured the bDMARD in the comparison. These results were not made clear in the summary. The authors mention that, similar to tofacitinib trials, they observed

"higher numbers of serious infection events in patients aged 65 years or older enrolled in the Medicare database than in younger patients from commercial databases" but do not explicitly state that this was also true for bDMARDs. Furthermore, incidence of serious infections with tofacitinib was not significantly different to that of bDMARDs in the older population and was significantly higher only when compared with etanercept in younger groups.

Favalli, in his Comment,<sup>2</sup> mentions that data from an ad-hoc analysis of an ongoing Phase 3b/4 trial (NCT02092467; data cut-off: August, 2019; database not locked; data subject to change) show "a significantly higher risk of serious and fatal infections in older patients (>65 years) treated with tofacitinib compared with tumour necrosis factor inhibitors" (TNFi), but we believe the commentary presents insufficient data for contextualisation. The incidence of serious infections was indeed increased in patients aged 65 years or older compared with younger patients, and this increase was greater with tofacitinib than with TNFi—but more so for tofacitinib 10 mg twice per day than for tofacitinib 5 mg twice per day, the widely approved dose.<sup>3</sup> The Comment refers to TNFi, giving the impression of a comparison with a broad group of drugs, yet only etanercept and adalimumab were studied.<sup>3</sup> It is important to assess the risk of serious infections with tofacitinib in the context of additional clinical and real-world data.

All authors are employees and stockholders of Pfizer and this Correspondence was funded by Pfizer. Medical writing support, under the guidance of the authors, was provided by Emma Deeks, CMC Connect, McCann Health Medical Communications, and was funded by Pfizer in accordance with Good Publication Practice 3 guidelines.

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## Tocilizumab in COVID-19: finding the optimal route and dose

The Tocilizumab in Patients with Severe COVID-19 Pneumonia (TESEO) study by Giovanni Guaraldi and colleagues<sup>1</sup> provides vital information regarding the benefits of tocilizumab in severe pneumonia due to COVID-19. However, certain aspects of the study warrant deliberation in greater detail.

By contrast with the pharmacokinetic and pharmacodynamic bioequivalence data available from non-COVID settings,<sup>2</sup> use of 324 mg of subcutaneous tocilizumab in patients with COVID-19 was found to be as efficacious as intravenous tocilizumab at a cumulative dose of 16 mg/kg. The difference in the therapy costs resulting from these cumulative doses (and the consumables involved in intravenous administration) could have substantial implications from a pharmacoeconomic point of view. Anecdotal signals of efficacy in COVID-19 have been reported previously with a single 162 mg dose of subcutaneous tocilizumab.<sup>3</sup> Dose optimisation of subcutaneous tocilizumab could thus be explored in future studies, as it has the potential to further reduce the cost of therapy.

Since short-term use of tocilizumab is not bereft of serious adverse events,<sup>4</sup> many of which are dose dependent, a comparative safety analysis of the subcutaneous tocilizumab group (which had a much lower cumulative