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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).[1] 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[1,2] (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 appendicectomy. 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,[3] 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.[4] 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,[5] 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.[3] Subsequently, anakinra has been proposed as a promising therapeutic option for preventing inflammation and delayed

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See Online for appendix

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[3] and sepsis[2] 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)[2] 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.

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