THE LANCET
Rheumatology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol* 2020; published online May 4. https://doi.org/10.1016/S2665-9913(20)30096-5.

Supplementary Information:

Contents: Details of reported cases of CSS (including sHLH/MAS) treated with intravenous anakinra (from Table 3)

1) A 36-year-old female with a background of schizoaffective disorder with a six month history of steroid-responsive high fevers, hypotension and hypertriglyceridemia and raised ferritin was extensively investigated and diagnosed with smouldering MAS associated with the myelodysplastic syndrome (MDS)[75]. Anakinra was initiated at a dose of 100 mg twice a day. The patient's mean arterial blood pressure stabilized, her fevers remitted, CRP normalized and steroids were tapered. The patient remained afebrile and hemodynamically stable for 2 months while receiving IV or SC (further details unknown) treatment with anakinra.

2) A 4-year-old girl, with JIA (diagnosed at 8 months) complicated by MAS received anakinra monotherapy at a dose of 11.2 mg/kg/day intravenously (5.6 mg/kg every 12 hours) in the intensive care unit[76,77]. She had good clinical response, albeit partial, and at 2 year follow-up, she was stable on combination biologic therapy with anakinra at 0.9 mg/kg/day, IV abatacept (every three weeks to control arthritis), methotrexate and monthly pulse corticosteroids.

3) A 20-year-old male, with no significant past medical history, was diagnosed with AOSD based on a two week history of fevers, myalgia, sore throat, truncal rash, mild hepatosplenomegaly, generalized lymphadenopathy and a ferritin of 18,500 ng/ml[78]. During the second week of hospital admission, he developed MAS, with unremitting fevers, pancytopenia, acute kidney injury and a consumptive coagulopathy, with a peak ferritin of 155,000 ng/ml and haemophagocytosis demonstrated on lymph node biopsy. Despite an initial transient response to high-dose pulsed IV methylprednisolone, the continuous fever returned, and the patient developed acute respiratory distress and a severe inflammatory response syndrome requiring intubation and inotropic support. During week 3 of hospital admission, anakinra 200 mg IV was administered. The patient rapidly defervesced, inotropes were weaned, and he was extubated 3 days later. Six days after starting anakinra, the dose and route of administration were changed to 100 mg/day SC with cyclosporine (100 mg twice daily). He was discharged from the hospital 12 days after initiation of anakinra with normal functional status, inflammatory markers and renal biochemistry and improving haematological parameters. Cyclosporine and prednisolone were tapered and methotrexate was introduced. The patient experienced a recurrence of symptoms when anakinra was inadvertently discontinued, but otherwise remained clinically well at the time of publication with normal inflammatory markers and ferritin, on a maintenance regimen of anakinra (100mg daily SC) and methotrexate (10mg weekly).

4) A 22-month-old boy with septic arthritis of the hip (*Candida Albicans* culture positive) was diagnosed with MAS on day 20, meeting six of eight diagnostic criteria: fevers, decreased fibrinogen, elevated triglycerides, bicytopenia, elevated ferritin, and elevated soluble interleukin-2 receptor (IL-2R)[79]. He was initially treated with oral prednisolone, in addition to antibiotics and anti-fungals, but was re-admitted two months later with recurrence of HLH (characterised by fevers with increased ferritin and triglycerides with reduced fibrinogen). IV anakinra (dose unspecified) was added, resulting in resolution of his symptoms (fevers and rash). He was discharged on prednisolone, anakinra and anti-

fungals and remained on anakinra at two-year follow-up. He was diagnosed with juvenile idiopathic arthritis (JIA), given the complete response to anakinra and recurrence after anakinra was stopped, despite no other joints becoming involved.

5) A 71-year-old with an ANCA positive vasculitis (with acute renal failure, necrotising cresenteric glomerulonephritis on renal biopsy and anti-MPO antibodies) was treated with prednisolone, cyclophosphamide, plasmapheresis and haemodialysis[80]. Two weeks following discharge, he was re-admitted with a pulmonary embolism and persistent fevers, leukopenia (which did not recover after stopping cyclophosphamide), deranged liver function tests and a ferritin of 18,569 ug/l. Bone marrow aspirate confirmed haemophagocytosis. He was diagnosed with HLH secondary to cytomegalovirus reactivation (CMV) and treated with IV ganciclovir (1.25 mg/kg after each dialysis session) and IV anakinra (400 mg/3 d IV) for 10 days. He recovered well from the acute illness, but remained on dialysis.

6) A 19-year-old female with recently diagnosed systemic lupus erythematosus (SLE), including pericardial tamponade and nephritis, presented weeks after diagnosis in shock and features of MAS. She had severe respiratory distress syndrome requiring high ventilator pressures resulting in bilateral pneumothoraceses. In addition, to antibiotics and anti-viral therapies, she received plasmapheresis for thrombotic thrombocytopenic purpura. She was in multi-organ system failure and received anakinra at maximal doses 48 mg/kg/day for 3 days but passed away within 2 weeks of hospitalization with multi-organ failure.

7) A previously healthy 8-year-old male with a 2-year history of nosebleeds presented with fever, rash, abdominal pain, vomiting, and deranged liver function tests. He received prednisone for the rash, and he was evaluated by oncologists. His labs revealed elevated sCD25 [21,288 IU (<1,105)] and notably decreased NK cell function (heterozygous for *STXBP2* mutations). He was hyperferritinaemic (8,740 ng/mL) and hypofibrinogenaemic, and he was started on the HLH-04 protocol (dexamethasone, cyclosporine, etoposide) for HLH. He was found to have significantly elevated HHV-6 levels, and ganciclovir was initiated. His condition markedly worsened with multi-organ failure and coma, and he was started on high dose anakinra (initially 8 mg/kg/day and eventually up to 48 mg/kg/day). He developed fungemia with *Candida parapsilosis* and eventually died one month after hospital admission.

8) A 16-year-old female with long-standing gastroparesis, with a central line for nutrition, and migraines was admitted to the hospital for fever, abdominal pain, and thrombocytopenia. She was found to have transaminitis, coagulopathy, and profound hyperferritinaemia (117,215 ng/mL). Biopsy specimens from bone marrow, liver, gut, and lung all revealed hemosiderin-laden macrophages. She was started on anakinra for presumed MAS (started at 4 mg/kg/day and eventually worked up to 48 mg/kg/day). In addition, she received high dose methylprednisolone but developed hypertension and PRES (posterior reversible encephalopathy syndrome). She had elevated sCD164 levels and absent NK cell function (heterozygous for missense *STXBP2* mutation). The

hyperferritinaemia improved as did her liver function tests and thrombocytopenia. Clinically, her encephalopathy resolved and ferritin declined to 556 ng/mL, but her abdominal pain, headaches, and hypertension persisted. Her ferritin began to rise again after approximately one month of hospitalization, and she remained on anakinra, methylprednisolone, and cyclosporine A. Abatacept was added without notable improvement and her ferritin rose to 79,493 ng/mL. Tocilizumab was added without significant benefit. She developed significant gastrointestinal bleeding and progressive multi-organ failure. After 3 months of hospitalization without any obvious infections, she was transferred to another tertiary care center for a second opinion. She developed aspergillosis and died a month later.