Is intravenous anakinra safe?

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Proposal:

In September 2018 the North Central London Joint Formulary Committee (NCL-JFC) reviewed anakinra for secondary haemophagocytic lymphohistiocytosis (sHLH). We were tasked with preparing a protocol for use. Here we summarize the rationale and safety data for using anakinra intravenously for a subset of patients.

Background:

sHLH / MAS is characterized by a fulminant cytokine storm which may lead to multiorgan dysfunction and high mortality. sHLH/MAS may complicate haematological malignancies, autoimmune disorders and infections. Interleukin (IL)-1 is pivotal to the aetiopathogenesis; a central autocrine loop of IL-1β over-secretion leads to a cytokine storm of IL-6, IL-18, ferritin, interferon-gamma and soluble CD163 (released from macrophages).

Anakinra is a recombinant humanized IL-1 receptor antagonist that inhibits both IL-1β and IL-1α. Anakinra is licensed in the UK for for Rheumatoid Arthritis (RA), Systemic Juvenile Idiopathic Arthritis (SJIA), Adult-Onset Still's Disease (AOSD) and Cryopyrin-Associated Periodic Syndromes (CAPS). The licenced dose is 100mg OD administered subcutaneously, however, anakinra has been generally safe and well tolerated when given by bolus intravenous injection or continuous infusion to healthy volunteers and patients with various underlying conditions (described below).

The assumption should be that anakinra is given subcutaneously unless contraindicated as platelets too low (<20), or concerns about absorption.

Intravenous Anakinra

The safety of intravenous anakinra, was evaluated in a phase I study where administration of anakinra to 25 healthy men in a three hour continuous intravenous infusion at doses of between 1 and 10 mg/kg did not produce clinically significant changes in complete blood counts, mononuclear cell phenotypes, blood chemistry profiles, or serum iron or cortisol levels[1].

Pharmacokinetic studies of anakinra in both subcutaneous and intravenous forms, have demonstrated a similar area under the curve (AUC) (reflecting the exposure to the drug after administration), for both a single dose of anakinra - subcutaneous 100mg anakinra and intravenous (1mg/kg) bolus injection in healthy volunteers (Table 1)[2]. The terminal half-life is longer subcutaneously (5.24 hours) than intravenously (2.64 hours), with similar clearance, suggesting that the absorption process is slower than the elimination process.

Anakinra is a large polypeptide, and such has a small initial volume of distribution. Anakinra is renally cleared and data from subcutaneous evaluation in patients with renal impairment, suggests that as renal function decreases, systemic exposure to anakinra increases[2]. According to the label, dose adjusting is not required in mild-moderate renal impairment in patients with RA.

Continuous infusions of anakinra may have advantages over bolus injections to rapidly attain and maintain a steady state plasma concentration. Continuous infusions of anakinra have been used anecdotally to manage cases of sHLH/MAS. Another advantage of using intravenous anakinra, may be improved blood brain penetration, although there is low permeation into cerebrospinal fluid[3,4].

Table 1 Pharmacokinetic comparison of single dose intravenous (IV) and subcutaneous (SC) administration of anakinra[2]

	IV (1mg/kg)	SC (100mg)
Subjects with normal renal function	12	6
Cmax (ng/mL)	22400	773
$t_{1/2}$ (h)	2.64	5.24
AUC (ng*hr/mL)	9590	10200
CL (mL/min)	137	170

Data are presented as mean values. Cmax, Maximum concentration; t1/2, terminal half-life; AUC, area under plasma concentration-time curve from time 0 to infinity; CL, plasma clearance

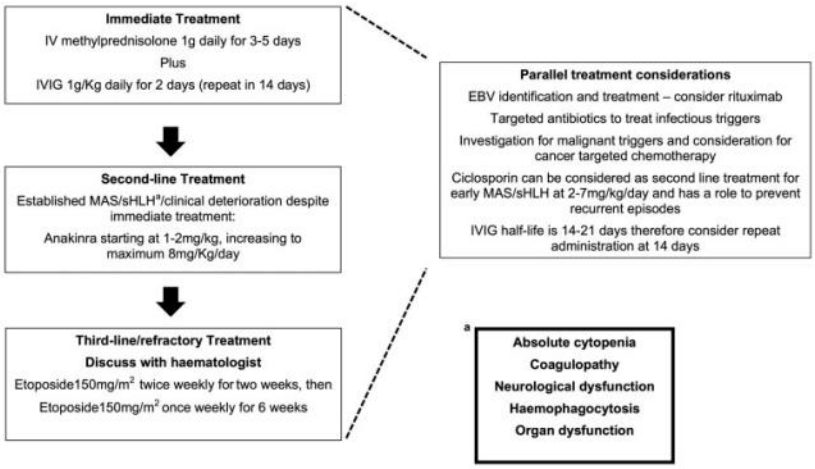
Haemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome:

Recommended treatment algorithms include anakinra as a second line therapy in established HLH/MAS (Figure 1), at a starting dose of 1-2mg/kg, increasing to a maximum of 8mg/kg/day[5]. It is important to highlight that doses of 100 mg four times daily of anakinra have been needed to achieve remission in refractory cases of MAS, highlighting that initial doses of 1-2 mg/kg may not be sufficient[6]. The route of administration of anakinra is not specified. Most reports in the literature describe the subcutaneous route. Although there is limited published evidence, intravenous anakinra is emerging as a safe and effective therapy for sHLH/MAS, with accumulating clinical experience, from consensus specialist opinion, both nationally (HASC meeting) and locally (HLH MDT at UCLH).

A recent publication demonstrated the successful use of intravenous anakinra. A 21 year old male, with MAS presented as fulminant liver failure, with clinical deterioration despite intravenous methylprednisolone, intravenous immunoglobulin, subcutaneous anakinra and liver transplantation[7]. Intravenous anakinra was initiated at a starting dose of 200mg daily,

escalated to 600mg daily. Treatment with anakinra was then escalated to intravenous formulation on the presumption of better absorption in the setting of liver transplant failure. Tacrolimus was added and anakinra continued at 600mg intravenously once daily for four weeks, with no direct adverse events documented. The patient was subsequently switched to subcutaneous anakinra (200mg) once the ferritin was <1000. The patient was successfully stepped down from the intensive care unit with good clinical outcome.

Figure 1. Recommended Treatment Algorithm for Patients with sHLH/MAS[5]



MAS: macrophage activation syndrome; sHLH: secondary haemophagocytic lymphocytosis.

Sepsis & Macrophage Activation Like Syndrome (MALS):

In a phase III randomized double blind trial comparing 1 or 2 mg/kg/hr with placebo, anakinra failed to meet the primary endpoint of improved 28-day survival[8], but did improve survival in patients with multi-organ dysfunction, a predicted mortality probability of >24% at study entry, or septic shock. Based upon these results, a subsequent confirmatory phase III trial was undertaken in patients with severe sepsis or septic shock[9]. In 350 patients with severe sepsis, anakinra was delivered by a 100 mg intravenous bolus followed by a 72 hour continuous infusion at a rate of 2 mg/kg/h[9]. Clinical and laboratory adverse event rates were comparable for the anakinra and placebo groups. This study was discontinued following an interim analysis, in which no survival benefits could be demonstrated. Twenty years after trial completion, retrospective review identified 43 patients (5.6% of the total enrolled) that could be classified has having MAS (with deranged liver function and disseminated intravascular coagulation). 26 of 43 patient were treated with intravenous anakinra and 17 with placebo; the 28-day mortality was 35 and 65%, respectively and this difference was statistically significant (p= 0.0006)[10]. These results suggest that a subgroup of carefully selected patients with sepsis and inflammation, Macrophage Activation Like Syndrome (MALS), may respond to immunomodulatory therapy with intravenous anakinra.

Although clinical trials of anakinra in sepsis, showed equivocal efficacy, they did not reveal either increased mortality rate or serious/non-serious adverse reactions in the anakinra treatment arms over placebo groups.

Safety of intravenous anakinra in other indications:

a) **Graft versus Host Disease:**

Anakinra was given by a continuous intravenous infusion at doses of 400–3200 mg daily for seven days to 17 patients with steroid-resistant acute graft versus host disease. A reversible rise of liver transaminases was seen in two of 17 patients, but the enzyme levels returned to normal after completion of anakinra treatment[11].

b) **Subarachnoid Haemorrhage:**

Anakinra was given as a 500 mg bolus, followed by a 10 mg/kg/hr infusion for 24 hours to six patients with subarachnoid haemorrhage[12]. There were no adverse or serious adverse events attributable to anakinra.

c) **Acute Stroke:**

In a randomised Phase II study of anakinra in acute stroke, 34 patients within 6 hours of the onset of symptoms of acute stroke were randomised to anakinra or matching placebo[13]. Anakinra was administered intravenously by a 100 mg bolus loading dose, followed by a 2 mg/kg/h infusion over 72 hours. No adverse events were attributed to anakinra, which was safe and well-tolerated.

Ongoing Trials of intravenous anakinra:

The PROVIDE trial (ClinicalTrials.gov NCT03332225) is a double-blind randomized clinical trial of personalised immunotherapy in sepsis (MALS), randomising patients to either placebo or intravenous anakinra 200mg three times/day for seven days. Treatment will be selected using a panel of biomarkers and laboratory findings to identify hyper- or hypo-inflammatory patient profiles. The study started in December 2017 and the estimated primary completion date is November 2019.

Summary

HLH is a hyperinflammatory syndrome, which if not promptly treated, can lead rapidly to critical illness and death. Anakinra is recommended in published sHLH management algorithms. Accumulating evidence and clinical experience supports the safe use of intravenous anakinra.

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