HIGHER-DOSE CANAKINUMAB THERAPY FOR REFRACTORY MACROPHAGE ACTIVATION SYNDROME IN CHILDREN WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS: TWO CASE REPORTS

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Resume. Macrophage activation syndrome (MAS) is a life-threatening, potentially fatal complication of systemic juvenile idiopathic arthritis (sJIA) appears in non-relieved fever, cytopenia, coagulopathy, liver and CNS dysfunctions. Triggers of MAS could be disease activity, infections and medications. Known IL-1 is the key cytokine in pathogenesis of MAS and SjIA, and disease flare associated with increased amounts of different cytokines, especially IL-1β. Many cases of MAS are medically-refractory to traditional doses of cytokine inhibition and may require increased dosing of biologic cytokine blockade. Interleukin-1 (IL-1) is typically a key cytokine in the pathogenesis of sJIA and associated MAS. When MAS occurs in the setting of sJIA treated with IL-1 inhibitors, then increased dosing of IL-1 blockers may be beneficial. This has been shown for anakinra, an IL-1 receptor antagonist, but this drug is currently not available worldwide. Another IL-1 blocker, canakinumab (CKB), is a monoclonal antibody that blocks IL-1β, but does not also block IL-1α like anakinra. Herein, we describe 2 sJIA patients who developed MAS on standard doses of CKB (4 mg/kg). Both patients received an increased dose of CKB: 150 mg (7.5 and 12.5 mg/kg, respectively) with rapid and complete resolution of MAS. Later the CKB doses was tapered to normal regimen. No side effects or adverse events were noticed during usage of increased CKB doses. Increased dosing of CKB should be considered for CKB-treated sJIA patients who develop MAS on standard dosing.

Key words: macrophage activation syndrome; systemic juvenile idiopathic arthritis; interleukin-1; anti-IL-1 treatment; canakinumab; monoclonal antibody.

BACKGROUND

Macrophage activation syndrome (MAS) is a sometimes fatal complication of rheumatic disorders, most commonly complicating sJIA in childhood [1, 17, 20]. MAS is related to familial hemophagocytic lymphohistiocytosis (HLH) which has been traditionally treated with high doses of etoposide chemotherapy [7].

Since MAS is not considered to be a result of homozygous mutations in cytolytic pathway genes, and because the HLH treatment protocol is associated with a high degree of mortality, rheumatologists have chosen to treat rheumatic disease associated MAS with non-cytotoxic immunosuppression. This typically includes a combination of high dose corticosteroids (CS), the calcineurin inhibitor, cyclosporine A, and, more recently, the addition of the recombinant interleukin-1 (IL-1) receptor antagonist (IL-1Ra), anakinra [17].

While lower doses of anakinra (1–2 mg/kg/day) may suffice to treat MAS associated with systemic juvenile idiopathic arthritis (sJIA) [3, 9, 12], when patients are already on anakinra, even higher doses may be required to control MAS [8–10]. In addition to anakinra, other IL-1 blocking agents are also available for treatment of sJIA [22]. Canakinumab (CKB) is a monoclonal antibody directed against IL-1β and has been shown to be highly effective in treating sJIA [19]. When MAS occurs in the setting of CKB treated sJIA, it is currently unknown whether or not increased dosing of CKB will help treat the MAS.

CASE PRESENTATIONS

Herein, we describe 2 patients with sJIA, who required higher than sJIA standard dosing of CKB to effectively resolve episodes of MAS that occurred despite standard doses of CKB.

Patient 1: An 11-month-old boy presented with prolonged fever, evanescent salmon-colored rash, knee arthritis, hepatomegaly, pericarditis, leukocytosis, and elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum levels of liver enzymes. sJIA with associated MAS was suspected and treatment with CS was initiated with a good response. Disease
Relapses occurred at the ages of 18 and 23 months after tapering doses of CS. IL-1 blockade was initiated with CKB as this was the only IL-1 blocker available in Russia.

After the first injection at the age of 25 months (standard dose of 4 mg/kg every 4 weeks) he had a good clinical response, and he weaned off CS. He did well until the 57th day after starting CKB (just before the 3rd CKB injection) when he presented with knee arthritis (no fever or rash) and increased CRP and liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)]. Within two weeks after the 3rd CKB injection, he presented with fever, rash, symptoms of enterocolitis, and liver enzyme elevation.

He was admitted to the hospital and had continued fever, hepatomegaly, diarrhea, and increased CRP, ALT, AST, lactate dehydrogenase (LDH), and ferritin. After several days of IV antibiotics, intravenous immunoglobulin (IVIG) (1 gr/kg), and pulse methylprednisolone therapy (30 mg/kg) followed oral CS, the fever and rash resolved, and the CRP, ALT, AST, LDH, and ferritin were decreased.

However, on the 9th day of admission the patient’s condition dramatically deteriorated. The fever and rash returned, and he developed pancytopenia, and increased CRP, ALT, AST, ferritin (16.932 ng/ml), and LDH (2.770 U/l), with decreased total serum protein (5.6 g/d), albumin (2.8 g/dl), and sodium (127 mmol/l).

His labs and clinical exam were consistent with coagulopathy, a hemorrhagic syndrome, and central nervous system dysfunction. Repeated courses of high dose (30 mg/kg) pulse methylprednisolone therapy, IVIG, fresh frozen plasma, and broad-spectrum antibiotics were ineffective.

Due to developing life-threatening resistant MAS,
CKB was administered at ~3-times the recommended dose (12.5 mg/kg). This resulted in a dramatic clinical improvement (fever and rash resolved within 3 days after the CKB injection), and normalization of his lab abnormalities within a week. No side effects from increased CKB were noted, and the patient was discharged to home 9 days post-CKB with a tapering regiment of oral CS. His hospital course and laboratory values are plotted and summarized in Figure 1 and Table 1. He has done well as is now receiving conventional CKB dosing (4 mg/kg every 4 weeks).

**Patient 2:** An 8-year-old girl with sJIA was doing well on CKB (4 mg/kg every 4 weeks) without the need of CS therapy. However, she developed a clinically mild form of MAS without signs of a sJIA flare (no arthritis or rash) just before her 9th CKB injection. One month before (at the time of the 8th CKB injection) she had mild anemia (Hb = 11.5 g/dl), leukopenia (WBC = 3.9 × 10³/mm³), and increased LDH (475 U/l), ferritin (412.3 ng/ml), and CRP (6.0 mg/l).

The diagnosis of MAS was considered, and CKB was injected at the standard dose (4 mg/kg). At the time of 9th scheduled CKB injection she had developed sore throat, lymphadenopathy, and low grade fever, but no rash or arthritis.

She continued to deteriorate clinically, and her liver laboratory parameters worsened: increased ALT (181 U/l), AST (131.8 U/l), and LDH (753 U/l). She received an increased dosage of CKB (~2-times normal, 7.5 mg/kg) for the scheduled 9th injection without corticosteroids. Her clinical and laboratory features of MAS resolved within a week without any noted adverse events. Her next CKB injection was in 28 days at a dose of 6 mg/kg and was then tapered to 4 mg/kg for the 10th monthly CKB injection. She continues to do well at this current dose of CKB.

As it is known sJIA is an autoinflammatory condition with a peak age of onset of 2 years of age [2] but can occur in the first 12 months of life like patient N 1 reported herein. MAS is a life-threatening complication of sJIA [17], and MAS is likely more common in children with sJIA than previously considered [1]. Diagnostically, MAS can be a challenge as many features are shared with sJIA flares, and MAS can be present at disease onset [2]. Unlike the HLH criteria [7], preliminary MAS criteria for sJIA include liver dysfunction [16], as was noted in both children reported herein. Typically, elevated serum ferritin is a sensitive marker of MAS [5]. However, with the increased use of IL-1 and IL-6 blockade in children with sJIA, the ferritin value may be blunted, even in the setting of MAS, and the ratio of ferritin to ESR may be of greater diagnostic utility [6]. For patient N 2 reported herein, the MAS presentation was associated with only a slightly elevated ferritin level, and clinically the prodromal stage leading up to MAS in both patients was longer than usual. Anecdotal...
ally, we have observed this phenomenon in others sJIA patients who developed MAS on biologic therapies. Moreover, we have noted severe organ damage during the MAS course that did not necessarily correlate well with ferritin levels. Thus, one must be aware of these diagnostic dilemmas so as to not delay appropriate MAS therapy in the setting of sJIA on biologic therapy.

As many as half of the cases of MAS are medically-resistant to standard dose sJIA therapy and frequently require more aggressive treatment: cyclosporine A, high dose CS, and cytokine targeted biologic medications [20, 21]. For many patients, IL-1 is a key cytokine in the pathogenesis of sJIA [14] and associated MAS [17], and disease flares have been associated with increased amounts of pro-inflammatory cytokines, particularly IL-1β. Theoretically, increased IL-1 production can overwhelm the body’s countering mechanisms (e.g. production of IL-1Ra). Anakinra is a recombinant version of naturally occurring IL-1Ra, and increased doses of IL-1Ra may be needed to bind excessive amounts of IL-1β. There are now several publications demonstrating the efficacy of increased anakinra dosing to treat MAS episodes [8, 18, 19]. Despite its documented benefit in treating sJIA [15], anakinra is not available in all parts of the world. However, two other IL-1 blocking agents have been studied as therapy for sJIA, CKB (a monoclonal antibody to IL-1β) [19] and rilonacept (an IL-1 receptor fusion protein) [11].

Currently, there is limited data regarding the use of CKB and rilonacept for treating MAS in the setting of sJIA. Indeed, there are only a few cases of MAS reported to occur during or after CKB treatment of sJIA in randomized controlled trials [19]. Herein, we report the use of increased doses of CKB in 2 children with sJIA treated with standard dose CKB for treatment of MAS. Both sJIA patients received one scheduled injection of an increased dose of CKB (150 mg, ~3-and 2-times standard doses, respectively) with rapid resolution of MAS allowing for tapering back down to standard CKB dosing of 4 mg/kg every 4 weeks. There were no notable short term adverse events consistent with the published safety and efficacy of high doses of CKB from clinical trials. For example, after a single dose of 10 mg/kg of CKB, free IL-1ß was reduced by more than 90% for more than 60 days [4]. In a subsequent long-term phase III extension trial, cryopyrin mutant patients with residual symptoms after the first CKB dose responded to an increased dose of up to 8 mg/kg and/or an increased dosing frequency [10]. As cytokine inhibitors target circulating or locally produced cytokines, there appears to be a larger therapeutic window for dosing of these medications compared to traditional medicines which directly target cells. One must also be careful to not always attribute (cause and effect) the development of MAS in the setting of cytokine inhibition to the therapy itself, as increased dosing of the same biologic medication may be highly beneficial in resolving the MAS.

CONCLUSIONS

sJIA and MAS are often both IL-1-driven conditions. MAS can occur in the setting of sJIA treated with standard dosing of IL-1 blockade by CKB. Our report provides evidence for the efficacy and safety of short term increased doses (2–3-times normal) of CKB in treating sJIA associated MAS. Further study of the efficacy and safety of increased doses of CKB for treatment of MAS in children with sJIA is warranted.

CONSENT

Written consent was obtained from the patient families for publication of these reports. Approval of higher-dose canakinumab treatment was obtained from the local ethical committee of Saint Petersburg State Pediatric Medical University.

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ПРИМЕНИЕ ПОВЫШЕННЫХ ДОЗ КАНАКИНАМБА ДЛЯ РЕФРАКТЕРНОГО СИНДРОМА АКТИВАЦИИ МАКРОФАГОВ У ДЕТЕЙ С СИСТЕМНЫМ ЮВЕНИЛЬНЫМ ИДИОПАТИЧЕСКИМ АРТРИТОМ: ДАННЫЕ ДВУХ СЛУЧАЕВ

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Резюме. Синдром активации макрофагов (САМ) — жизнеугрожающее, потенциально фатальное осложнение си-
стемного ювенильного идиопатического артрита (сЮИА), проявляющееся в виде постоянной лихорадки, цитопане, коагулопатии, дисфункции печени и ЦНС. Тригерами САМ могут быть активность основного заболевания, инфекции, лекарственные препараты. Известно, что интерлейкин-1 является ключевым цитокином в патогенезе САМ и сЮИА, антагониста интерлейкина-1, одном из препаратов может быть полезным. Это ранее было показано терапии блокаторами интерлейкина-1, повышение доз этих препаратов может быть полезным. Это ранее было показано для антагониста рецептора интерлейкина-1, однако этот препарат является недоступным во многих странах мира. Другой блокатор интерлейкина-1 — канакинумаб — моноклональное антитело, нейтрализующее интерлейкин-1β, но не связывающее интерлейкин-1α, подобно анакинре. В данной статье мы описываем 2 пациентов с сЮИА, развивших САМ на фоне стандартных доз канакинумаба (4 мг/кг). Оба пациента получили повышенные дозы канакинумаба: 150 мг (7,5 и 12,5 мг/кг, соответственно) с быстрым и полным разрешением САМ. Позже, дозы канакинумаба были возвращены к исходным. Не было зафиксировано побочных и нежелательных явлений, связанных с применением повышенных доз канакинумаба. Применение повышенных доз канакинумаба следует рассматривать как одну из терапевтических возможностей у пациентов, получающих канакинумаб и развивающих САМ на фоне применения стандартных дозировок канакинумаба.

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**Ключевые слова:** синдром активации макрофагов; системный ювенильный идиопатический артрит; интерлейкин-1; терапия блокаторами ИЛ-1; канакинумаб; моноклональные антитела.

[Информация об авторах]