Successful treatment with B-cell depleting therapy for refractory systemic onset juvenile idiopathic arthritis: a case report

Sir. Juvenile idiopathic arthritis (JIA) is a common disease of childhood, which often persists through adulthood. Up to 10% of JIA patients are severely disabled or handicapped [1]. Patients with systemic onset JIA (SOJIA) compose 10–15% of all cases of JIA. Unfortunately, about one-third of children with SOJIA develop a progressive refractory disease resulting in severe disability despite the diverse therapeutic approaches available nowadays [2]. Macrophage activation syndrome is a severe life-threatening complication of SOJIA with a propensity to occur following a bacterial or viral infection or after initiating therapy [3].

We present an 18-yr-old female patient with SOJIA who was refractory to almost all possible modes of therapy, yet remitted following the administration of two consecutive doses of rituximab.

An 18-yr-old woman with a 12-yr history of refractory SOJIA was admitted due to an active disease. During the years her disease was systemically active and involved multiple joints, such as shoulders, hips, knees, ankles, wrists and PIP joints. She was treated with several DMARDs such as MTX (4 yrs), cyclophosphamide (6 months), IFQ (8 yrs), cyclosporin (1 yr) and thalidomide (6 months), yet no clinical benefit was achieved. Later on intravenous immunoglobulins were administered (6 months) as well as the anti-TNF agents etanercept (1 yr), infliximab (6 months) and the anti IL-1 agent anakinra (3 months), but she was not able to sustain a stable clinical remission. A year prior to this hospitalization she was admitted to the intensive care unit in shock due to an abrupt development of the macrophage activation syndrome. Her ferritin levels were above 30 000 in shock due to an abrupt development of the macrophage activation syndrome. Her ferritin levels were above 30 000 and her serum ferritin and D-dimer concentrations were 42 000 mg/dl and 26 000 ng/ml during that episode.

During the following year lab results still indicated a highly active disease, with CRP levels up to 20 mg/dl, ESR was 60 mm/1 h and haemoglobin level was 9.0 g/dl. Her functional condition steadily deteriorated and she could no longer stand or walk being incapacitated by severe hip pain and her numerous joint deformities. Due to this active and refractory condition the patient was maintained solely on a weekly high dose infusion of methylprednisolone (300–500 mg) for over a year. Attempts to wean her from this high-dose steroid therapy promptly resulted in a transient increase of the number of swollen and tender joints with a parallel escalation of inflammatory indices. Her physical examination revealed numerous joint deformities but no signs of active synovitis. Her Tanner stage was 2 for breast development and pubic hair pattern with concurrent primary amenorrhoea. The long-standing steroid therapy led to severe osteoporosis (T-score –4.7), and several vertebral pathological fractures, with significant cushingoid features.

After being treated with steroid therapy for over a year, two infusions of rituximab 1 g on days 1 and 15 were administered. The patient was given concomitant MTX (12.5 mg/week) that was replaced 2 months later on with daily AZA (100 mg) due to severe nausea. Concomitant treatment consisted of methylprednisolone 150 mg, trimethoprim sulphamethoxazole, oestrogen therapy, bisphosphonate with supplemental high-dose vitamin D therapy and calcium due to undetectable levels of vitamin D.

The patient was gradually weaned from the weekly high-dose methylprednisolone to weekly dosages of 30 mg/dl (Fig. 1). Within several weeks the patient reported a marked functional improvement with a significant decrease of the intensity of her joint pain. Along with decreasing the corticosteroid dose her cushingoid appearance gradually disappeared and her physical therapist was able to initiate weight-bearing activities.

The patient is currently enjoying a sustained remission lasting 18 months with no evidence of systemic inflammation or active synovitis. Her CRP concentration had continuously decreased from 20 mg/dl to 1.5 mg/dl, haemoglobin level increased from 9 g/dl to 12.0 g/dl and her serum ferritin and D-dimer concentrations entirely normalized (Fig. 1).

B-cell depletion using rituximab is becoming widely accepted as an effective therapeutic modality in adult patients with RA whose disease is insufficiently controlled by MTX or TNF inhibitors [4, 5]. Two cases of successful treatment with B-cell depleting therapy were reported previously in patients with refractory polyarticular JIA and adult onset Still’s disease [6, 7]. For these reasons we elected to use rituximab in a patient with SOJIA with a refractory and steroid-dependent disease.

There is evidence, although not specific, supporting the role of B cells in JIA pathogenesis; plasma cells and Th-2-related cytokines, such as IL-4 and -10 are present in high concentrations as shown in synovial specimens obtained from JIA patients [8]. Wouters et al. [9] reported that in patients with SOJIA there was no increase in the activation or differentiation markers on T cells, but a profound decrease in circulating NK cells with coexisting hypergammaglobulinemia consistent with B-cell hyperactivity.

To the best of our knowledge this is the first reported case of successful treatment of SOJIA with rituximab in the English medical literature. Since B-cell depletion therapy is considered relatively safe, it may present a true alternative to conventional immunosuppressive and biological treatments in SOJIA. Future studies are needed to clarify the role of B-cell involvement in SOJIA and the possible advantages of B-cell depletion in these patients.

**Disclosure statement:** The authors have declared no conflicts of interest.

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A case of immune reconstitution syndrome: adult-onset Still’s disease in a patient with HIV infection

Sir, A 22-year-old homosexual man presented systemically unwell in March 2006, was diagnosed with HIV infection [baseline CD4 32 cells/mm³ (7%), viral load 589 708 copies] and commenced on highly active anti-retroviral therapy (HAART) with abacavir, lamivudine and ronavir/lopinavir. Twelve days later, the patient presented with new symptoms of sore throat, fever, rigor, myalgia, asymmetrical large joint arthralgia and morning stiffness. He reported diarrhoea since starting anti-retroviral therapy, but denied ocular or genital symptoms. He had no relevant past medical, family or travel history. Examination revealed effusions of rash, fevers, sweats, synovitis and elevated liver transaminases. He reported that AOSD may be a reactive phenomenon triggered by infectious agents and have found elevated levels of IgM and IgG antibodies against viruses (mumps, parainfluenza, rubella, Coxsackie B4, echovirus 7, adenovirus, influenza A, herpes viruses, hepatitis B, parvovirus B19, EBV, CMV) and bacteria (Yersinia enterocolitica, Mycoplasma pneumoniae, Chlamydia pneumoniae, Brucella abortus, Borrelia burgdorferi) [2]. Infection alone is unlikely to be sufficient to trigger AOSD and it is likely that a predisposing genetic background is needed, but to date no specific genetic polymorphisms have been demonstrated.

Evidence is accumulating to suggest that AOSD is a T-cell-driven disease [3]. Immune dysregulation, including abnormalities of T-cell number and function is a major feature of HIV infection. Additionally, the commencement of HAART leads to a release of naive T-cells (CD4⁺ and CD8⁺), increases in the CD4⁺ to CD8⁺ ratio and cytokine levels and precipitates imbalance of the TH1/TH2 profile [4, 5]. In 10–40% of the patients [6], these changes can precipitate the onset or provoke the deterioration of infectious, malignant and autoimmune conditions, the phenomenon of ‘immune reconstitution inflammatory syndrome’ (IRIS). IRIS is thought to result from rapid, marked restoration of pathogen-specific immune responses (to infectious or non-infectious antigens) usually within the first 8 weeks of HAART [4]. Risk factors include low CD4 count, presence of latent infection and marked virological and immunological response to HAART [6]. Although IRIS was first described in relation to infections, such as tuberculosis or CMV, there is increasing recognition of autoimmune conditions including SLE, RA and ReA [6].

In our patient, the clinical presentation of acute AOSD within 12 days of commencing HAART is highly suggestive of IRIS. There have been three previous case reports of AOSD in HIV but these occurred in the pre-HAART era and therefore could not implicate IRIS [7, 8].

In the context of HIV infection, the management of this patient with AOSD has proved complex. Glucocorticoids are potentiated by ritonavir and therefore conservative daily doses (prednisolone 20 mg) were used initially. The patient experienced a dramatic response within 1 week. However, the course of both the AOSD and HIV were unrelenting and refractory with episodic recurrence of rash, fevers, sweats, synovitis and elevated liver transaminases. While the liver dysregulation responded to increased prednisolone (35 mg), the CD4⁺ count deteriorated to 89 cells/mm³ and therefore tenofovir was added. Symptoms relapsed each time that prednisolone was reduced (<15 mg daily).

The therapeutic challenges posed by concurrent HIV infection and autoimmune/inflammatory disease have been described [6, 9]. In the context of IRIS, a recent review including nine cases of rheumatic disease suggests a favourable outcome following treatment, with the exception of a patient with SLE whose symptoms flared with steroid taper [10]. Although early reports suggested rapid deterioration of immunity among HIV patients treated with DMARDs, successful use has now been reported in treatment of malignancies and organ transplantation [9]. Given this, and the patient’s hepatic dysfunction, mycophenolate mofetil was added. Currently, the patient is tolerating a dose of 1000 mg mycophenolate mofetil daily without immune compromise and has returned to work on 5 mg prednisolone daily.

This case of AOSD, arising rapidly after commencement of HAART for HIV infection, is most likely explained by immune reconstitution syndrome. AOSD remains a poorly understood chronic rheumatic syndrome characterized by dysregulation of