inhibition. Moreover, a combination of biomarkers including WBC, CRP, ferritin and LDH may be useful for the diagnosis of flare.

A lack of biomarkers during tocilizumab treatment in inflammatory diseases has been a problem for clinical practice. Especially for large vessel vasculitis and adult-onset Still's disease, the evaluation of disease activity is more dependent on acute-phase reactants in blood tests than RA. Our study showed that the CRP levels reflected disease activity under treatment with an IL-6 inhibitor only slightly, as was expected. Alternatively, LDH was identified as a potential biomarker to detect flare. LDH is an enzyme that exists abundantly in reticulocytes, the heart, lungs, muscles and liver, but is distributed in almost all types of organ cells. We assume that LDH elevation in active adult-onset Still's disease not only reflects liver involvement, but also is derived from systemic inflammation of multiple organs, caused by inflammatory cytokines. Indeed, LDH elevation has been reported to be relevant to systemic inflammation [6, 7] and macrophage-activated syndrome [8]. Another important suggestion of our study was that a very subtle increase in CRP levels could indicate worsening in adult-onset Still's disease under tocilizumab treatment. The CRP level at relapse in tocilizumab(+) was only 0.1 mg/dl, but the increase from 0.01 mg/dl before relapse was significant.

Our data is not confirmatory, due to the nature of a retrospective study with a small sample size; however, we believe that serum LDH is a promising biomarker for flare in adult-onset Still's disease treated with an IL-6 inhibitor. Since adult-onset Still's disease is a rare disease, and a flare during anti-IL-6 treatment is much rarer [4], cooperation to accumulate cases is necessary to validate our data.

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Hiroki Yamada[1], Yuko Kaneko [1], Hiroya Tamai [1] and Tsutomu Takeuchi[1]

[1]*Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan*

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Correspondence to: Yuko Kaneko, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. E-mail: ykaneko.z6@keio.jp

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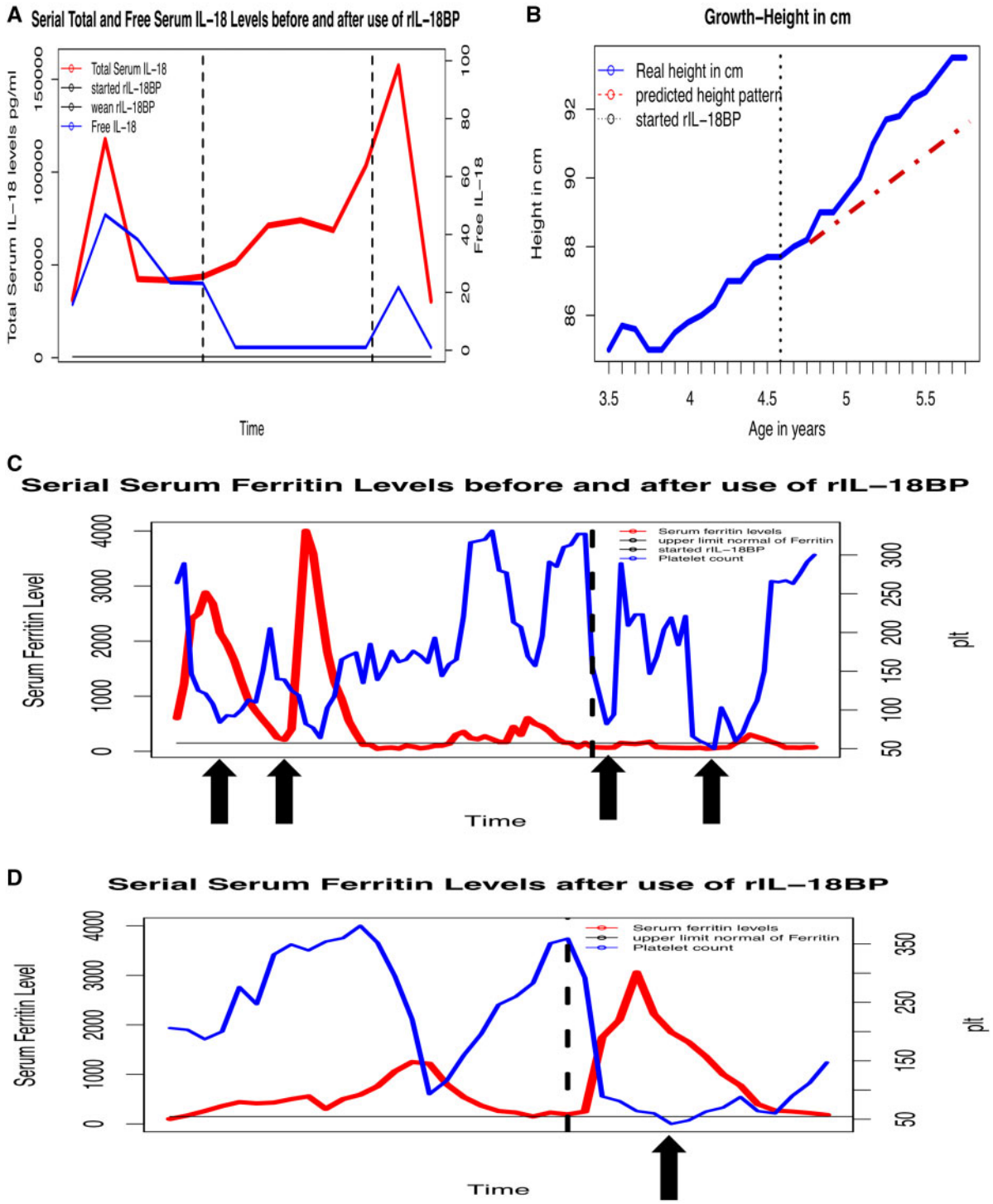
IL-18 as therapeutic target in a patient with resistant systemic juvenile idiopathic arthritis and recurrent macrophage activation syndrome

Rheumatology key message

- Use of rIL-18BP in refractory sJIA was well tolerated with reduced MAS frequency and severity.

Sir, Patients with systemic JIA (sJIA) are at high risk for macrophage activation syndrome (MAS) [1]. IL-18 is a proinflammatory cytokine elevated in sJIA and Adult Onset Stills Disease, and may represent a pathogenic link between sJIA and MAS [2, 3]. IL-18 is counterbalanced by its high-affinity endogenous antagonist, IL-18 binding protein (IL-18BP) [4]. Based on this, many authors suggested using exogenous IL-18BP as a novel

FIG. 1 rIL-18BP use in a patient with severe sJIA and MAS



(**A**) Total and Free IL-18 levels over time. Vertical lines: start (left) and missed dose (right) of rIL-18BP therapy. (**B**) Linear growth change over time and after start of rIL-18BP. Actual height shown in blue. Vertical line: start of rIL-18BP treatment, red line: predicted height based on pre-treatment growth velocity. (**C** and **D**) Serial platelet counts (blue) and serum ferritin levels (red) before and after rIL-18BP treatment and MAS flare after missed dose. Vertical black line indicates start of treatment (**C**) and change in rIL-18BP dosing interval (**D**). Arrows point to MAS episodes. sJIA: systemic JIA; MAS: macrophage activation syndrome.

therapeutic approach for inflammatory diseases [4, 5]. A recent Phase II trial of recombinant IL-18BP (rIL-18BP-Tadekinig alfa) showed promising results for Adult Onset Stills Disease [6]. Here, we report the first use of rIL-18BP in a patient with refractory sJIA and recurrent MAS.

We report a 6-year-old mixed race male diagnosed at age 14 months with sJIA. His subsequent course was complicated by recurrent MAS episodes requiring pulse (30 mg/kg/day) steroids for 3 days followed by daily prednisolone at 2 mg/kg/day, and ciclosporin 5–7 mg/kg/day in order to control episodes. He failed to achieve remission despite numerous non-biologic and biologic medications including anakinra, canakinumab, IVIG, tocilizumab and rituximab. Despite this, he continued to have frequent flares and recurrent MAS with any attempts to wean steroids. Fourteen months into his illness, he was diagnosed with interstitial lung disease in the setting of persistent tachypnoea and erythematous finger clubbing. His biopsy subsequently showed features of pulmonary alveolar proteinosis and lipoid pneumonia.

Laboratory findings during disease flares and MAS episodes showed classic features including persistently elevated ferritin levels and total serum IL-18 levels up to 117 346 pg/ml. Corresponding free IL-18 levels during disease flares and MAS episodes were elevated up to 46.82 pg/ml (most healthy individuals have undetectable levels but can be up to 5 pg/ml [2]) (Fig. 1A).

Given the patient's persistently elevated total and free IL-18, he was started on rIL-18BP (tadekinig alfa) under a compassionate-use investigational new drug authorization, 2 mg/kg subcutaneously every 48 h, with continuation of previous therapy. Immediately prior to the start of rIL-18BP, his total IL-18 was 43 724 pg/ml and free IL-18 was 23.17 pg/ml. His free IL-18 levels were undetectable 24 h after the first dose (Fig. 1A).

Over the first year of treatment, he slowly improved clinically, and oral steroids were tapered from 2 mg/kg/day to 0.75 mg/kg/day while continuing other medications (ciclosporin, anakinra (switched from canakinumab later in the course), monthly IVIG). He showed signs of stable disease including increased growth velocity from 1.75 cm/year before initiation of rIL-18BP to 5.75 cm/year after rIL-18BP (Fig. 1B). As detailed below, MAS episodes after initiation of rIL-18BP were controlled with IV methylprednisolone only, without the need for increase in oral steroids or ciclosporin.

He was diagnosed with MAS triggered by parainfluenza-3, 4 weeks after starting rIL-18BP. He was febrile but otherwise appeared clinically well despite typical laboratory findings of MAS (Fig. 1C). Remarkably, his ferritin level remained normal. Several months later he developed another MAS episode triggered by gastroenteritis. This episode similarly only required three IV steroid pulses, and was again noted that ferritin levels did not exceed 250 ng/ml (Fig. 1C).

One year later, he developed persistent productive cough with mild hypoxia (95–96%). Although extensive infectious evaluation was negative, he was suspected to have pneumonia and improved after broad-spectrum antibiotics. With concerns about rIL-18BP contributing to lung infections, an attempted medication wean was started by decreasing frequency of injection. The patient did not receive a dose for four days (first missed dose) and promptly developed a severe MAS episode, which required six doses of IV steroid pulses, increasing baseline ciclosporin, anakinra and daily steroid dose. Notably, this episode showed marked elevation of ferritin level for the first time since initiation of rIL-18BP (Fig. 1D). It is likely that this was triggered by lung infection and exacerbated by missing one dose of rIL-18BP. In addition, free IL-18 levels, previously undetectable, increased to 21.8 pg/ml at the time of MAS onset. He has since resumed rIL-18BP at 3 mg/kg every 48 h with clinical stabilization, decrease in free IL-18 to undetectable levels, and allowing restart of a steroid taper.

In summary, use of IL-18BP was associated with stabilization of disease course and reduced MAS severity, but also notable improvement of linear growth with steroid wean. Levels of free IL-18 were undetectable shortly after initiation of rIL-18BP, although total serum IL-18 levels remained elevated, consistent with other studies and suggesting that free IL-18 might be a more accurate biomarker for disease activity [2, 7]. The hypothesis of balance between IL-18 and IL-18BP is also well supported by mouse models of MAS [7, 8]. This is interesting in light of our clinical experience, where the first missed rIL-18BP disrupted that balance, and was followed by immediate development of MAS. This is also in agreement with recent findings that IL-18 both distinguishes and promotes MAS [7]. This report raises hope for treating diseases marked by excessive free IL-18 such as sJIA, and preventing progression to MAS.

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Shima Yasin[1], Krista Solomon[1], Scott W. Canna[2], Charlotte Girard-Guyonvarc'h[3], Cem Gabay[3], Eduardo Schiffrin[4], Andrew Sleight[4], Alexei A. Grom[1] and Grant S. Schulert[1]

[1]*Division of Rheumatology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH,* [2]*Pediatric Rheumatology & Immunology, Children's Hospital of Pittsburgh/UPMC, Pittsburgh, PA, USA,* [3]*Rheumatology, Geneva University Hospitals and University of Geneva, Geneva and* [4]*AB2Bio, Lausanne, Switzerland*
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Correspondence to: Grant S. Schulert, Division of Rheumatology, MLC 4010, Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229, USA.
E-mail: Grant.schulert@cchmc.org

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Successful treatment of complicated pericarditis after myocardial infarction with interleukin-1 blocker

Rheumatology key message

- Targeting IL-1 could be a novel therapy in pericarditis associated with inflammasome activation after myocardial injury.

SIR, We report the case of a 66-year-old man admitted to the Coronary Care Unit of the Santa Maria della Misericordia Hospital of Udine, Italy, for subacute inferior-posterior myocardial infarction, and later developing a complicated pericarditis and severe systemic inflammation. The patient had a negligible medical history, except for a right hip replacement 2 months before.

The day before admission, a new onset of chest discomfort was recorded. The following day during a cardiologic evaluation ECG showed inferior Q waves and a small r wave in V1 with persistent ST-elevation, and T wave inversion in the inferior and in V5-V6 leads (Fig. 1), consistent with recent myocardial infarction. The transthoracic echocardiogram confirmed inferior and posterior walls akinesia with preserved global systolic function and mild pericardial effusion without signs of tamponade. Invasive coronary angiography was performed and demonstrated an occlusion of a posterolateral coronary branch and a critical stenosis of the proximal circumflex artery, which was treated by percutaneous transluminal coronary angioplasty with drug-eluting stent. During the following days a growing pericardial and pleural effusion occurred, with high grade fever (up to 39.5°C) and severe systemic inflammation (CRP 28, 5 mg/dl, procalcitonin 0.53 ng/ml). Autoimmunity (ANA, anti-dsDNA, ENA, RF, ACPA and ANCA), anti-phospholipid antibodies and microbiological analyses (including blood haemocultures) were all negative, and empirical therapy with high doses of acetylsalicylic acid (i.e. 1000 mg daily) plus antimicrobial therapy with levofloxacin and piperacillin/tazobactam were administered, however without any benefit.

Then, colchicine was started, again without any clinical improvement, and persistence of fever, pleuro-pericardial effusion and systemic inflammation. After 2 weeks of persistent systemic inflammation with fever, high levels of CRP (15–16 mg/dl), pleuro-pericardial effusion and progressive rest dyspnoea in the last 2 days, an inflammasome activation resistant to conventional therapy was supposed. To avoid CS, anti-IL-1 therapy with anakinra was then started, at the dosage of 100 mg/day. Fever disappeared in 12 h, and chest pain in 4 days. Levels of CRP abruptly decreased and completely normalized within 10 days of treatment. Pericardial effusion significantly improved in <5 days, decreasing from 20 mm to <5 mm (Fig. 1).