Interleukin-6 receptor antagonist use in systemic juvenile idiopathic arthritis: a case report

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ABSTRACT

Systemic onset Juvenile Idiopathic Arthritis (JIA) accounts for approximately 4-15% of JIA, and has the worst prognosis. Treatment option in SJIA is still limited. Interleukin-6 receptor antagonist is the second line therapy, has been used widely in adult rheumatoid arthritis patients, but no report of pediatric population in Indonesia. To report the efficacy of interleukin-6 receptor antagonist-Tocilizumab in difficult to treat SJIA management. An 11-years old boy was diagnosed with SJIA and treated with Ibuprofen, then switched to high dose pulse steroid therapy, continued by weekly methotrexate for 6 weeks, however flare up color the clinical manifestation. Following ACR Guideline 2013, tocilizumab every 2 weeks was started. After 4 weeks, the MD Global scores reduced from 10.7 to 3, ACR 70 was achieved, no systemic manifestations were found with normal lab result. Tocilizumab shows beneficial effects in SJIA patient.

Keywords: Interleukin-6 antagonist, systemic juvenile idiopathic arthritis


INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is defined as persistent arthritis in 1 or more joints for at least 6 weeks if certain exclusionary conditions have been eliminated, in children under 16 years old. The overall prevalence approximately 30-150 per 100.000.1-3 There are 3 major subtypes of JIA based on the symptoms at disease onset and are designated systemic, oligoarticular, and polyarticular onset.2

Systemic JIA (SJIA) accounts for approximately 4-15% of JIA and is defined as arthritis in ≥ 1 joint preceded by fever of at least 2 weeks duration that is documented to by daily for at least 3 days and accompanied by one or more of the following: evanescent eryhematous rash, generalized lymphadenopathy, hepatosplenomegaly, and serositis.2,3

Compared to other type of JIA, SJIA has the worst prognosis. Many children with SJIA have a particularly refractory course, with persistent disease associated with a high risk of joint damage and severe growth impairment.5,8

The cause and pathogenesis of JIA, however is still poorly understood. Both genetic and environmental components appear to play a role. The inflammatory process underlying SJIA appears to be distinct from other categories of JIA, with a central role for both interleukin-1 (IL-1) and interleukin-6 (IL-6).9,11,12
The goal of therapy for SJIA focuses on the prompt control of active inflammation and symptoms and the prevention of a number of disease- and/or treatment-related morbidities such as growth disturbances, joint damage, and functional limitations.9 Because none of the available drugs has curative potential, the primary therapeutic goal is to control symptoms and to avoid joint damage.9,11,12

With the advent of biologic disease-modifying anti-rheumatic drugs (DMARDs), commonly referred to as biologics, the treatment options for JIA have changed and improved markedly. Biologics are genetically engineered drugs that work by selectively blocking the effects of cytokines.11-19 Multiple biologics have been approved for the treatment of rheumatoid arthritis (RA) in adult patients.22,23 The use of biologics in pediatric population are still limited in Indonesia. This paper reports a case of biologics agent, interleukin-6 receptor antagonist use in a SJIA patient.

ILLUSTRATION CASE

IBSKP, an 11-years old boy, came to Sanglah Hospital on February 2015 with chief complaint fever, pain and swollen knees and feet. He experienced fever since 4 weeks before admission. The fever is high all day, with a peak reaching 40°C in the early morning. The temperature fell temporary after antipyretic administration to raise after few hours. No rash in the skin found when the temperature is high. Appetite reducing since the onset of fever. And his body weight reduced. The urination and bowel habit was normal.

Pain and swelling in his both knees and feet felt since 2 months before admission starting with numb in toes, spread to all fingers, and knees. Patient unable to walk nor do any other daily activities normally. Painkiller only temporarily reducing pain. No complains of nausea, vomiting, double or blurred vision.

Four months before the swelling of the joints, patient once complaining fever for more than 1 weeks, with hyperleukocytosis, which leads the suspicous of malignancy. The immune-phenotype result, however, was negative. The blood culture test shows infection of Pseudomonas aeruginosa spp and he was treated with antibiotic for 14 days.

Patient was the second child in the family, parents has divorced when he was 4 years old, father experienced depression, the care taker was his aunt. His older sister is healthy. Two cousins of grandmother was diagnosed with Systemic Lupus Erythematosus, and one of them died in the age of 22 years.

Patient was born spontaneously with body weight of 3000 grams, length of 50 cm, appropriate for gestational age, had exclusively breastfed for 6 months, start feeding soft food at 6 months, and adult food at the age of 1, growth and developmental status was normal. As he is on the 4th degree in elementary school, school report was average and socialized with his peers normally before the onset of the disease.

On February 2015, diagnosis of SJIA was made from the clinical manifestation and laboratory findings leukocytosis, thrombocytopenia, anemia, major increase of ESR and C-Reactive Protein. The ANA test was positive with negative rheumatoid factor. Patient first treated with ibuprofen, then changed to glucocorticoid (GC) with high dose methylprednisolone which results in disappearance of fever and arthritis. After 6 weeks, left superior palpebral was dropped, a head MRI was done showing cerebral ischemia. The second high dose methylprednisolone was instituted, resulted in relieves of the complains. Similar symptoms manifest the next month, as he suffered from fever, headache, swelling of joints, followed by multiple lymph node enlargement, hepatomegaly, and splenomegaly. The laboratory result shows leukopenia, anemia, thrombocytopenia, high ESR. Treatment option started with GC, but only helps to reduce the fever for 1 week. Methotrexate (MTX) 10 mg/body surface area once a week, was added after controlling hemoglobin level by blood transfusion. This regimens helped reducing the size of joint swelling. As the headache and fever remain disturbing patient sleep and activity of life, we concluded patient need to start the second line of disease management.

According to the American College of Rheumatology Guideline 2013, JIA management characterized into two major groups, those with active systemic features and those without systemic features. The recommendations for initiation of various therapeutic agents are according to the Active Joint Counts (AJC) or MD Global.

The patient was given GC as first line therapy, fever reduced, but joint swelling and pain was persist. When GC was tapered off, the fever recurred even when MTX was added and the joints size reduce. As the fever remain until 4 weeks, a decision to start the next treatment option, IL-1 inhibitor, Anakinra, or IL-6 inhibitor, tocilizumab. Anakinra was not available in Indonesia and the family refuse the use of anakinra. Tocilizumab which used quite frequent in Rheumatic Arthritis adult patients, was available in Indonesia and family agree to start with. Tocilizumab was given intravenously, 12mg/kg, every 2 week. Results showed improvement in
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almost all aspect of the disease, i.e: patient had no complains of headache nor pain in joints. The temperature start on normal range, the joint swelling relieve. Liver and lymph node return to normal size. All laboratory result were normalized. Patient was then discharged and continuing medication for every 2 weeks. MD Global score which was use as the monitoring, shows improvement, where on the first day of the disease the MD Global Score was 10.7, after two weeks decreasing to 6, and at week 4 the MD global was 3.

**DISCUSSION**

In our setting, SJIA is rare, and fatal outcome is common in previous year without opportunity to start second line treatment as it is costly and unaffordable for most patients. Identification of SJIA mostly form clinical aspects by exclusions of other possible diagnosis, such as malignancy. Clinical manifestation of SJIA are arthritis in many different joints, systemic features such as fever, hepatomegaly, splenomegaly, lymph node enlargement. Involvement of cardiac, neural, and eye also found in some cases. Laboratory finding shows pancytopenia, high ESR, positive rheumatoid factor and ANA test. In our case, patient came with fever for more than 3 weeks, pain and swelling in joints for more than 6 weeks, lymph node enlargement, hepatomegaly and splenomegaly. The fever was quotidian in pattern, peak in the morning, with rash in skin and severe headache. The laboratory result shows leukopenia, anemia, thrombocytopenia, raised of ESR, low fibrinogen. The patient diagnosed with SJIA after exclusion of malignancy which showed very similar clinical manifestation.

ACR guideline 2013 recommended SJIA treatment is started with conventional Disease Modifying Anti Rheumatoid Drugs (DMARDs) such as NSAID, Glucocorticoid, Methotrexate and Biologic Agents, such as Interleukin-1 antagonist receptor, Interleukin-6 antagonist receptor, or Interleukin-12 antagonist receptor antagonist. In our case, first line treatment using NSAID, glucocorticoid, and methotrexate failed in sustaining good clinical outcome. Treatment option refer to use tocilizumab rather than anakinra, due to availability and agreement of family Tocilizumab, an interleukin-6 receptor antagonist, was started at 12 mg/kg body weight intravenously every 2 weeks.

Monitoring of the disease includes pGALS (Pain, Gait, Arms, Legs, Spine) score, MD (Medical Doctor) global score, ACR percentage. In our case, we use the MD Global Score and ACR percentage to see the improvement of the disease. MD Global score reduced from 10.7 to 3. ACR 70% also achieved by the end of monitoring. The patient able to walk without supports. Appetite increased, as well as body weight increased by 500 gram after two injections of tocilizumab.

**SUMMARY**

An eleven-years old boy, with SJIA, fail to maintain remission from initial treatment (with NSAID, high dose methylprednisolone followed by methotrexate), was successfully got better quality of life with tocilizumab an interleukin-6 receptor antagonist. Tocilizumab was given 12 mg/kg every 2 weeks, in our case for 4 weeks. MD Global Score, reducing from 10.7 to 3 on the first week, and ACR 70 achieved after the second administration of the drug. After 4 weeks of administered dose able to walk normally and gain weight by 500 grams in 1 month.

As conclusion, tocilizumab shows beneficial effects in patient with systemic juvenile idiopathic arthritis

**REFERENCES**

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