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Canakinumab (ILARIS®) in cryopyrin-associated periodic syndrome (CAPS) patients below 2 years of age: Review of four cases and literature.

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Abstract

Cryopyrin-Associated Periodic Syndrome (CAPS) is combination of different auto-inflammatory hereditary disorders with same genetic basis. CAPS caused mostly due to mutation of *NLRP3* gene (nucleotide-binding domain, leucine-rich family (NLR), pyrin domain containing 3), which is an early onset in children. There are many anti-INF agents, anti-IL blockers have been reported in the literature, and continuous efforts are being made to find more effective and safe biological drugs. Canakinumab (ILARIS®) is a biological medicine approved to treat a group of rare, but severe, inherited autoimmune disorders associated with over-secretion of IL-1. In preclinical and clinical examinations, canakinumab has been reported as an effective IL-1β blocker in patients of all ages, but available clinical data in children below two years is limited. In this study, we presented four recently reported cases and reviewed available literature that demonstrated the efficacy and safety profiles of canakinumab in patients with CAPS and other autoimmune and inflammatory disorders.

Keywords: Canakinumab, Interleukin, Deficiency, Cryopyrin-associated periodic syndrome, Monoclonal antibody, Biological drug

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Introduction

Canakinumab is a human monoclonal antibody which blocks the interleukin-1β (IL-1β) with no cross reactivity with other variants of the interleukin-1 (IL-1) family. Canakinumab (ILARIS®) was developed by Novartis Pharmaceuticals initially for the treatment of rheumatoid arthritis but US Food and Drug Administration (USFDA) approved the drug for the treatment of cryopyrin-associated periodic syndromes in June 2009, subsequently, European Medicines Agency approved canakinumab in October 2009 [1,2]. Canakinumab acts as a neutralizing agent of IL-1β signaling that leads to suppression of inflammation in a spectrum of autoimmune syndromes such as Cryopyrin-Familial Cold Auto-inflammatory Syndrome (FCAS), Cryopyrin-Associated Periodic Syndromes (CAPS), Muckle-Wells syndrome (MSW) and Neonatal-Onset Multisystem Inflammatory Disease (NOMID) [3,4]. In 2016, FDA approved canakinumab for treatment of three more rare disorders namely- Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) and Familial Mediterranean Fever (FMF) [5].

In previous studies it has been observed that the therapeutic response significantly improved by addition of canakinumab in patients with rheumatoid arthritis with no safety concerns [6,7]. Moreover, in acute gout patients, single dose (subcutaneous 150 mg) of canakinumab showed better results in pain relief and joint swelling. However, it has been observed that by blocking the pro-inflammatory cytokine interleukin-1β, canakinumab subsequently leads to adverse effects such as reduction in rates of recurrent myocardial infarction, stroke, and cardiovascular impairments and high risk of death in heart attack patients [8-10].

Several studies demonstrated that the genetic basis of CAPS associated syndromes, symptoms (fevers and urticarial rash,) and clinical manifestations (arthropathy, sensorineural hearing loss, central nervous system inflammation) are similar. Available treatment options such as oral anti-inflammatory drugs, corticosteroids were used to manage the symptoms but improved patient outcomes and quality of life have not been reported as expected. Despite the fact that canakinumab can cause side effects, preclinical and clinical studies reported that canakinumab is effective in treatment of CAPS patients of all age groups. Based on accumulated clinical evidences, canakinumab showed significant efficacy and safety profiles in patients aged ≥ 4 years, but limited reports are available on canakinumab effectiveness in patients below

2 years of age [3,11-13]. In this review, four recently reported pediatric cases explained in detailed and reviewed available literature on biological therapeutics that are effective IL-1 blockers and concluded with a comparison.

Case 1 [14]

The study was explored the efficacy of canakinumab in patient's ≤ 4 years of age and to evaluate pharmacokinetics and pharmacodynamics. Patients confirmed with cryopyrin-associated periodic syndrome aged 44 days to 4 years received open label canakinumab 2 mg/kg every 8 weeks for 56 weeks and for neonatal-onset multisystem inflammatory disease patients an initial dose of 4 mg/kg was administrated. Patients who were unable to achieve complete response upon injection were eligible for dose up titration (stepwise up-titration regimens of 4, 6 or 8 mg/kg s.c)

Total 17 patients were enrolled (6 were less than 24 months; mean age 7 months) administrated 2 mg/kg up to 12 mg/kg of canakinumab (s.c) based on body weight every 8 weeks (1 patient received doses of 4-6 mg/kg once weekly). For 6 NOMID patients, 5 were dosed with 2 mg/kg and 1 given 4 mg/kg (up titrated to 8 mg/kg at last dose). It was observed that in patients <24 months old were similar across the 6 patients from 44 days to 15 months Canakinumab was normalized through concentrations at steady state.

The results reported that canakinumab is an effective treatment for CAPS patients aged 44 days old and also pharmacokinetics results demonstrated that dose-normalized canakinumab exposure in patients <2 years old was similar to patients >2 years.

Case 2 [15]

A 28 months old boy (born at 38 week, by cesarean delivery) who diagnosed with NOMID since he was 60 days and commenced canakinumab treatment on 70th day as soon as an urticarial rash appeared. Upon genetic testing, it was further validated with a mutation in exon 3 of the *CIAS1/NLR3* gene, which is regarded to be *de novo* mutation, since it was not a characteristic of parents of patient. Treatment started with canakinumab at a dose of 4 mg/kg, higher than the recommended dose for older age. Anti-IL-1β monoclonal antibody treatment continued for >2 years and the patient remained without recurrence of disease or other complications.

The case indicated that early diagnosis of NOMID/CINCA syndrome and medication with IL-1 blockers as soon as possible for the improvement of the prognosis of cryopyrin-associated periodic syndrome gives better outcomes.

Case 3 [16]

This is an open-label phase I/II study, with an objective to study the efficacy and safety of escalating doses of canakinumab neonatal-onset multisystem inflammatory disease (NOMID). Six patients enrolled in this study for 24 months and underwent anakinra withdrawal. All the patients were received an initial s.c canakinumab dose was 150 mg (or 2 mg/kg in patients ≤ 40 kg) or 300 mg (or 4 mg/kg) with escalation up to 600 mg (or 8 mg/kg) every 4 weeks.

The observations at 6 months visit after initial dose administration showed that none had full remission, 4/6 achieved inflammatory remission, none has achieved CNS remission; but at the last study visit, 5/6 patients achieved inflammatory remission and 4/6 had continued CNS leukocytosis. No adverse events observed; however, hearing loss occurred in 1/10 ears. This study results support the argument that canakinumab improved symptoms and serum inflammatory features of NOMID can be achieved with canakinumab.

Case 4 [17]

This case study investigated and successfully immunized a patient with neonatal-onset multisystem inflammatory disease (NOMID) by using sufficient antibody titer under canakinumab therapy without complications. A 4 month old girl (spontaneous vaginal delivery, birth weight 2340 g, length was 46 cm) with a rash immediately after birth and worsened 4 months later, admitted to the Toho University Hospital. The family of child has no history of such rash, autoimmune disorders and periodic fever. After all clinical and physical examinations, with a prior consent, the patients underwent a genetic test. The results showed a *de novo* heterozygous mutation in the *NLRP3* gene, subsequently reported CAPS due to the disease-causing mutation.

A positive clinical response was noted (complete disappearance of rash and periodic fever) after canakinumab injection (2 mg/kg). After the patient met the Japanese clinical study criteria, canakinumab was administered as a single 2 mg/kg dose once every 8 weeks via subcutaneous injection. As an outcome of the follow-up, the patient started walking at the age of 15 month and demonstrated normal psychomotor development. In follow up, the suction sputum culture showed *S. pneumoniae* and *B. catarrhalis* at 13 months old and *H. influenzae* type B at 15 months old, respectively; however, there is no severe infection found in the patients.

This study reported that canakinumab is effective and safe in infants with NOMID/CINCA (Chronic Infantile Neurologic Cutaneous Articular) syndrome; moreover, successfully immunized the patient with live-attenuated vaccines concomitantly with canakinumab treatment.

Discussion

CAPS is a combination of group of rare, severe and inherited autoimmune disorders such as MWS, FCAS, NOMID, CINCA, etc., in which over secretion of IL-1 is a characteristic feature. Many animal model studies have been reported the administration of antibodies

against IL-1 protects from inflammation and decrease the histopathological events. IL-1 is one of the important cytokine that promotes the damage associated with RA by contributing destruction of cartilage, bone and periarticular tissues. Therefore, naturally occurring IL-1 receptor antagonist that bind and block the biological effect of IL-1 is essential. Over the past decade, there is an increased interest in use of biologic disease-modifying anti-rheumatic drugs and biological response modifiers based on the improved knowledge of roles of pro-inflammatory cytokines and interleukins. Since 2001, a new biological response modifier named 'Anakinra' is available for RA treatment. Many clinical studies showed that either alone or in combination with methotrexate anakinra improves the clinical signs and symptoms of the patients with significant safety profiles. Moreover, studies reported that anakinra is more effective in patients than that of anti TNF-agents [18-20]. Over last few years, studies on anakinra continuously show significant effectiveness with high safety profiles in patients with systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, hereditary auto-inflammatory syndromes, Schnitzler's syndrome, NOMID and in gout [21-23]. Moreover, studies also reported that anakinra is effective in treatment of adult-onset Still's disease by decreasing hematologic, biochemical and cytokine markers and produces rapid reductions in systemic and local inflammation [24,25]. More or less, anakinra is first ever IL-1 blocker approved for the treatment of RA; however, it showed significant effectiveness with remarkable safety profiles with CAPS associated disorders. The main adverse event observed in anakinra treatment is mild injection-site reactions; especially, in children, also Anakinra is not approved for children younger than 18 years of age.

In 2008, USFDA approved Rilonacept (IL-1 Trap/ Arcalyst™) with an "Orphan Drug" status for the treatment of CAPS disorders, FCAS and MWS, in adults and children aged 12 years and older. Rilonacept is a dimeric fusion protein that binds to the IL-1 receptor components and prevents interaction with cell surface, by which reduce the inflammation [26-28]. The initial clinical trials have been demonstrated that upon administration of rilonacept the patients showed significant decrease in disease-related symptom scores along with reduced serum amyloid A and CRP levels. Nevertheless, during the trials six adverse reactions- injection-site reactions, upper respiratory tract infections, sinusitis, cough, hypoesthesia, nausea, diarrhea, stomach discomfort, and urinary tract infections were reported. Moreover, rilonacept should not be administrated in combination with TNF-blocking agents, other IL-1 antagonists or vaccines [29,30]. In 2012, FDA advisory panel due to the significant risk of side effects than the benefits not recommended rilonacept for treatment of gout patients [31].

ILARIS® is a monoclonal antibody and the third most biological agent next to rilonacept and approved by FDA to treat cryopyrin-associated periodic syndrome in adults and children aged ≤ 4 years [3,32]. The pharmacokinetics and pharmacodynamics studies showed that fast and sustained remissions were observed in patients received Canakinumab, with lower incidences of adverse effects [33]. Simulation studies have confirmed that 150 mg canakinumab administration once in every 4 weeks, improved ACR scores (ACR score is a scale to measure the changes in rheumatoid arthritis symptoms and named after American College of Rheumatology) in patients with Rheumatoid Arthritis (RA), but no additional benefit was provided by higher doses or more frequent administration. Antiinflammatory therapeutic approach centering interleukin-1β in innate immunity pathways, treating with canakinumab (150 mg every 3 months) led to significant reduction in occurrence of cardiovascular events [34-36]. Subcutaneous (s.c) canakinumab administration at dose of once in every 8 weeks showed persistent disease control in patients with CAPS. In addition, canakinumab administration (s.c) at the dose of 150 mg in every 8 weeks showed significant tolerance and provided considerable disease control in children and adults across all CAPS phenotypes [37,38]. An interesting phenomenon reported that the canakinumab administrated during pregnancy in a patient with Muckle-Wells syndrome crossed the placenta. Subcutaneous (s.c) administration of canakinumab potentially induced rapid and sustainable response in pediatric patients either at a dose of 2 mg/kg or 150 mg [39,40]. Dose-normalized canakinumab administration in patients <2 years old was parallel to the patients >2 years. Early diagnosis of NOMID/CINCA and treatment with canakinumab improved the prognosis of CAPS patients. Symptoms and serum inflammatory features of NOMID were significantly improved with canakinumab at various doses. This indicates that canakinumab is effective and safe in infants with NOMID/CINCA syndrome [14-17,32]. It is not the age of the patients but the clinical phenotype, which is the main variable and determines the need of more frequent administration of the drug at advanced doses. Children and adults living with CAPS could have an improved outcome by treat-to-target strategies. Long-term treatment with canakinumab achieved a highly relevant improvement in the physical, emotional, and social lives. Canakinumab is safe, expensive and effective treatment for CAPS in children with improved health-related quality of life. However, sustained IL-1 suppression can be achieved by canakinumab, vigilance is necessary to diagnose the development of adverse events, especially, to identify associated infections [41-45].

In comparison, Canakinumab has several advantages than the other approved drugs such as anakinra and rilonacept. Anakinra and rilonacept block the signals of both IL-1α and IL-1β, while canakinumab shows high specification to IL-1β and does not interfere the pathways activated by IL-1. In addition, the half-life of canakinumab is longer

than that of other biological agents; therefore, frequent administration with increased doses is not essential. As far as CAPS treatment is concern, canakinumab is need to be administrated once in every two months, whereas, rilonacept and anakinra need to be administrated weekly and daily, respectively. The development of such biologic therapeutics for treatment of IL mediated autoimmune and inflammatory disorders is never ending research field, for example, Xoma-052 (XOMA), is a recently reported IL-1beta blocker and under evaluation for the treatment of cytokine mediated autoimmune and inflammatory disorders [46,47]. Withdrawal of anakinra treatment lead to regression of the symptoms within days, whereas administration of a dose of canakinumab once in 2 months showed persistence disease control in most of the CAPS patients by producing sustained IL suppression [33,41-45,48,49]. Most importantly, canakinumab can be used for the patients aged ≤ 4 years [3], while anakinra is approved for children older than 18 years of age and rilonacept children older than 12 years of age. This clearly indicates that owing to the limited adverse effects reported, canakinumab is the most effective biological therapeutic alternative for CAPS patients of all ages [26].

Conclusion

In conclusion, canakinumab is a reliable option for treatment in patients with CAPS across age groups. The reports showed that canakinumab is successful in achieving sustained clinical remissions and normalization. Treatment of CAPS and associated auto-inflammatory disorders is being a challenge for many years, more particularly, patients with below two years of age. The recent developments in biological agent therapy raise the hope, for instance, canakinumab is effective across all diseases including CAPS, RA, TRAPS, HIDS, MKD, FMF, etc. Though, canakinumab is an effective agent and approved for treatment of many rare disorders, there are significant limitations reported in clinical studies. The major challenge is lack of adequate sample sizes, therefore, measured outcomes and adverse events are not significant. In future, studies with large sample sizes and multi-centric data analyzing approaches are necessary to identify accurate effectiveness and side effects. Overall, canakinumab is a promising therapeutic biological agent for many hereditary diseases with improved patient outcomes, quality of life and safety.

Conflict of Interest

No clinical study was conducted in any of the cases mentioned in this article but reviewed available literature from biomedical databases such as PubMed and PMC central. Author has no potential conflict of interest to disclose.

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