

## Case Report

# Effects of A Humanized Anti-human IL-6 Receptor Monoclonal Antibody on Nakajo-Nishimura Syndrome

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### Short title

Nakajo-Nishimura Syndrome Treated with A Humanized Anti-human IL-6 Receptor Monoclonal Antibody

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### ABSTRACT

Nakajo-Nishimura syndrome (NNS) is a very rare hereditary disorder that has its onset in infancy with pernio-like skin rashes, and is accompanied by remittent fever and nodular erythema-like skin eruptions. The treatment of NNS is still under groping. Recently we encountered a case that was treated by corticosteroid and a humanized anti-human IL-6 receptor monoclonal antibody. As a result, the fever and skin rash was not improved sufficiently, and clinical symptoms of fat atrophy and joint contracture were gradually progressing. We herein report the effects of these agents and discuss the possibilities of new treatment direction.

**Keyword:** Nakajo-Nishimura Syndrome (NNS); Anti-human IL-6 Receptor Monoclonal Antibody; Autoinflammatory Disease; Proteasome-associated autoinflammatory syndromes (PRAAS)

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## 1. Introduction

Nakajo-Nishimura syndrome (NNS) (NNS; OMIM #256040, ORPHA2615), which has been reported uniquely in Japan, is an autosomal recessive inherited disorder caused by mutations in the PSMB8 gene<sup>[1,2,3]</sup>. Patients with this disease show pernio-like skin rashes since infancy, and they gradually develop partial lipodystrophy mainly in the face and upper extremities, as well as characteristic long clubbed fingers with contracture of the interphalangeal joints accompanied by remittent fever and nodular erythema-like skin eruptions. Recently we encountered a case that was treated by corticosteroid and a humanized anti-human IL-6 receptor monoclonal antibody. We herein report the effects of these agents and discuss the possibilities of new treatment direction.

## 2. Case Report

A 37-year-old Japanese female visited our department 10 years ago because of a periodic fever syndrome-like symptom. Her parents are cousins. All relatives are asymptomatic.

At 6 months of age, she had pernio-like purplish lesions with induration of about 1 cm in diameter appeared symmetrically in the hands and feet, which was an episode in November. At 10 months, the heat up to 39° C of unknown origin appeared. Even though it periodically appeared, the general condition was well. At 11 months, a nodular erythematous lesion appeared on the face. At 2 years of age, a gait difficulty due to the pain of both gastrocnemius muscle appeared and the induration in the muscle was noticed. Pathological myositis was confirmed by muscle biopsy. Although she had a shortening of Achilles tendon due to the cusped position, muscular strength was normal and no developmental disorders appeared. During junior high school days, fingers and long clubbed fingers and bones have been revealed. Hyperhidrosis of limbs and heliotrope-like erythema were accompanied. The interval of fever gradually became longer, and it appeared once a month with no incentives in particular in high school days. Knee

and shoulder joint pains appeared after entering university, and a small amount of corticosteroid was administered from the age of 24, but fever persisted and gradual leaning was progressing. From the age of 27, she visited dermatologic department of Wakayama Medical University Hospital because of a periodic fever syndrome-like disease.

At the age of 29 and 33, she gave birth of a low birth weight baby twice at the Caesarean section, but the frequency of fever rather prematurely decreased during pregnancy. There were no abnormalities in her infants.

### 3. Blood examination (at the age of 31)

Routine blood examinations were almost as follows; WBC 8300/ $\mu$ l (neu 78%, lym 19%, mono 3%), RBC 419 $\times$ 10<sup>4</sup>/ $\mu$ l, Hb 9.6g/dl, Ht 32.3%, Plt 31.9 $\times$ 10<sup>4</sup>/mm, AST 34IU/l, ALT 16IU/l, LDH 324IU/l,  $\gamma$ GTP 19IU/l, TP 8.8g/dl, Alb 2.9g/dl, Glb 5.9g/dl, T-bil 0.3mg/dl, TG 136mg/dl, T-cho 129mg/dl, Cre 0.42mg/dl, BUN 15mg/dl, UA 5.2mg/dl, Na 138mEq/dl, K 4.2mEq/dl, Cl 105mEq/dl, Fe 12 $\mu$ g/dl, CK 421IU/l, CRP 9.21mg/dl, ESR 88mm/h, 128mm/2h, amyloid A 1047 $\mu$ g/ml, ferritin 1564ng/ml.

Autoantibodies and cytokines are as follows; anti-nuclear antibody x320 (homogenous), RF 5.0IU/ml, anti-dsDNA antibody 11.3IU/ml, anti-Sm antibody (-), anti-SS-A/Ro antibody (-), anti-SS-B/La antibody (-), anti-cardiolipin antibody 2U/ml, MMP-3 31.7ng/ml, IgG 4049mg/dl, IgA 426mg/dl, IgM 254mg/dl, IgE 26157U/ml, TNF $\alpha$  5.5pg/ml (0.6~2.8), IL-1 $\beta$  16pg/m(<10), IL-6 50.8pg/m (<4), IFN $\gamma$  0.6IU/ml (<0.1).

Computed Tomography examination revealed the calcification of head and hepatosplenomegaly was pointed out by the ultrasound scan. At the age of 24, a contrast MRI of the previous doctor confirmed a diffuse myositis image with the contrast effect at T2 high in the thigh muscle.

### 4. Clinical diagnosis

This case satisfied all diagnostic criteria of NNS. *PSMB8* gene mutation was identified by whole genome homozygous junction mapping<sup>[1]</sup>.

### 5. Treatment and course

A small amount of prednisolone (from 4mg to 9mg per day) was continued, and her general condition improved slightly but did not change remarkably. Under the approval of the Ethics Committee of Wakayama Medical University, at first tocilizumab (320mg per 3 weeks), a humanized anti-human IL-6 receptor monoclonal antibody, was administered intravenously 23 times from the age of 34. After that, tocilizumab (320mg per 2 weeks) was continuously administered subcutaneously until now. Although CRP decreased to some extent and awareness of muscle pain was reduced, the high value of IFN-induced chemokine IP-10 was sustained, and the effect on fever and skin rash was not improved sufficiently. Fat atrophy and joint contracture were gradually progressing (**Figure 1**).



**Figure 1;** Clinical symptoms. Pernio-like skin rashes, partial lipodystrophy in the face and upper extremities, as well as long clubbed fingers.

## 6. Discussion

Autoinflammatory disorders caused by the dysfunction of proteasomes have been collectively designated as proteasome-associated autoinflammatory syndromes (PRAAS)<sup>[4,5]</sup>. PRAAS includes NNS, in which the elevation of the serum concentration of several proinflammatory cytokines and chemokines was reported such as IL-6, IP-10 and MCP-1<sup>[1]</sup>.

Based on our report, tocilizumab, a humanized anti-human IL-6 receptor monoclonal antibody, was administered for this presented patient. It inhibits the action of IL-6 and shows the immunosuppressive effects<sup>[6,7]</sup>. Tocilizumab is used for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis and so on. The anti-human IL-6 receptor monoclonal antibody prepared by mouse is modified to humanized chimeric antibody by genetic recombination technology. It binds preferentially to IL-6R over IL-6. Since IL-6 is a cytokine that plays an important role in the immune response and is involved in many diseases such as autoimmune diseases, multiple myeloma, prostate cancer etc., tocilizumab improves these diseases. However, the therapeutic effect was limited to this presented patient. On the other hand, Ishikawa reported an NNS case who showed good responses in fever, CRP and malaise to tocilizumab administration<sup>[8]</sup>.

As a conventional and standard treatment, corticosteroids and /or methotrexate are reported to be useful of effective<sup>[9]</sup>. They reported that the administration of oral corticosteroids and methotrexate were remarkably effective on laboratory findings and skin lesions.

Very recently, Honda-Ozaki and Kanazawa reported the pluripotent stem cell model of NNS untangles proinflammatory pathways mediated by oxidative stress and found a specific ROS-mediated inflammatory pathway, providing a platform for the discovery of alternative therapeutic options for NNS and related immunoproteasome disorders<sup>[10]</sup>. Individual case studies using iPS cells will develop new effective treatments.

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## Conflict of Interest

We have no conflicts in this report. This case was published in Japanese (Visual Dermatology 16: 141-143, 2017) as an invitation article.

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