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Efficacy of Etanercept with Jaw - Training for Rheumatoid Arthritis with Firstly Temporomandibular Joint Symptoms: A Case Report

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Abstract

Some patients with Rheumatoid Arthritis suffer with Temporomandibular Disorders (TMD). A 36-year-old Asian female presented to our hospital with Temporomandibular Joint (TMJ) symptoms, including pain. The maximum self-opening distance was 23 mm at first visit. As symptoms were worse in the morning and also started occurring in other joints, rheumatologists were consulted. The rheumatologists prescribed Etanercept (ETN), a tumor necrosis factor inhibitor which is commonly used in the early stages of Rheumatoid Arthritis (RA). The use of ETN together with conservative therapy for the TMJ improved the symptoms in the affected joints. No therapy for TMJ symptoms in RA patients has yet been established. However, the findings of this case suggest that the usage of biological products from the early stage of RA and jaw-training may be possible to manage TMJ symptoms.

Keywords: Temporomandibular joint, Rheumatoid arthritis, Biological products, Tnf inhibitor, Etanercept.

Abbreviations: RA-Rheumatoid Arthritis, TMD-Temporomandibular Disorders, TMJ-Temporomandibular Joint, ETN-Etanercept, EULAR-European League Against Rheumatism, MTX-Methotrexate, DMARDs-Disease-Modifying Anti-Rheumatic Drugs, JIA-Juvenile Idiopathic Arthritis, OA-Oral Appliance, NSAIDs-Non-Steroidal Anti-Inflammatory Drugs, MP-Metacarpophalangeal, SASP-Salazosulfapyridine, PSL-Prednisolone, PD FSE-Proton-Density Fast Spin-Echo, RF-Rheumatoid Factor, CH50-Complement Activity, MMP-3-Matrix Metalloproteinase 3, ESR-Erythrocyte Sedimentation Rate, CRP-C-Reactive Protein, NRS-Numeric Rating Scale, HCA-Hemolytic Complement Activity, TNF-Tumor Necrosis Factor inhibitors.

Introduction

The incidence of Rheumatoid Arthritis (RA) is 0.5-1% of the global population [1]. According to the Ministry of Health, Labor and Welfare, an estimated 700,000-800,000 people in Japan suffer from RA. It is three times more common in women than men, and usually develops between the ages of 30 to 50. The life expectancy of patients with RA is 20% lower than that of the general population. RA is a progressive condition, where inflammation causes joint destruction and synovial proliferation (pannus) around the articular cartilage. Symptoms include pain, tenderness, swelling and morning stiffness, often in the small joints of the hands and feet.

In 2010, the European League Against Rheumatism (EULAR) published new classification criteria for RA [2]. Table 1 shows the different areas that are evaluated and scored. When the total score is 6 or higher, the patient is diagnosed with RA.

Early diagnosis and medical treatment helps to prevent joint destruction. For the management, Methotrexate (MTX), anti-rheumatic drugs, including Disease-Modifying Anti-Rheumatic Drugs (DMARDs), and biological products such as Tumor Necrosis Factor inhibitors (TNF) or humanized anti-IL-6 receptor antibodies are all used. Among RA patients, some have TMJ symptoms. Bessa-Nogueira, et al. [3] reported that 70% of patients with RA had some TMJ symptoms, while Trenwith and Beale [4] noted that 62% of RA patients complained of TMJ symptoms at least once. Condylar volume and ramus height get smaller in Juvenile Idiopathic Arthritis (JIA) patients, which is one of the rheumatic disease in childhood [5]. At the moment, TMJ symptoms of RA patients seems to be little agreement as to how to manage in such cases **(Table 1)**.

Scoring system for RA	score
A. Joint involvement	
1 large joint	0
2−10 large joints	1
1−3 small joints (with or without involvement of large joints	2
4−10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Duration of symptoms	
<6 weeks	0
≥6 weeks	1
D. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR 0	0
Abnormal CRP or normal ESR 1	1

Table 1: Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA), Rheumatoid Factor (RF); Anti-Citrullinated Protein Antibody (ACPA); C-Reactive Protein (CRP); Erythrocyte Sedimentation Rate (ESR).

Case Report

A 36-year-old Asian female presented to the university of Tokyo hospital with pain in the left TMJ. She had been aware of sound produced by the left TMJ from around the age of 11, but had not experienced any pain or restricted opening. She became aware of the pain in the left TMJ one year before she first presented, and it had become sustained one month before presenting. The pain was worse in the morning and was less intense in the evening. Her past medical history included insomnia, pyelonephritis and infertility. Physical examination revealed multiple findings. There was facial asymmetry of the face **(Figure1A).**

Figure 1A: Facial photo with mouth closed (left) and opened (right).

The maximum self-opening distance of the mouth was 23 mm, and the forced-opening distance was 28 mm. Misalignment of the mandible was seen on the left side when opening. Pain and tenderness were experienced during movement of the left joint. Crepitus was observed in the left TMJ. Redness of the oral mucosa and gingiva was noted, but there was no swelling **(Figure 1B).**

Figure 1B: Oral photos at first visit.

Orthopantomography showed no deformity of the mandibular condyle. MRI revealed a joint disc derangement without reduction of the left TMJ. On the basis of these findings, a primary diagnosis of TMJ arthralgia and joint disc derangement without reduction was made. Treatment of these TMD was with an Oral Appliance (OA) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). We used stabilization appliance for reducing TMJ pain. Further symptoms were reported soon after the TMJ symptoms had begun **(Figure 2A, 2B).**

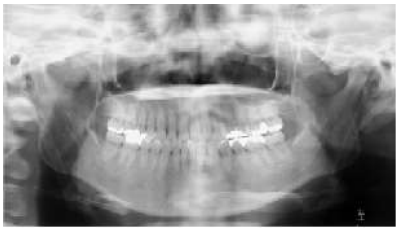

Figure 2A: Orthopantomography at first visit.

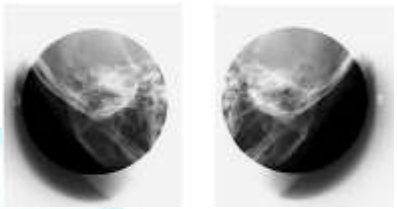

Figure 2B: Orbito-ramus projection at first visit.

The right shoulder became difficult to abduct. Moreover, pain in the Metacarpophalangeal (MP) joint of the second finger in the left hand appeared. Pain and swelling in the left third finger MP joint and pain in both feet thumb also appeared. At this time point, we consulted the allergy and rheumatology team, and a second diagnosis of RA was made. Using the new classification system for the diagnosis of RA, the swelling and pain of 4 joints was counted as 3 points, anti-cyclic citrullinated peptide antibody was 19.5 HU/ml and was counted as 3 points, and symptoms over 6 months was counted as 1 point. The total score was more than 6 points, which confirmed a diagnosis of RA. By the rheumatology team, she was started drug therapy for RA. Salazosulfapyridine (SASP), ETN and Prednisolone (PSL) were selected in order. SASP is a DMARD which is used globally in the treatment of RA [6]. ETN, a biological product, is also used to treat RA [7]. PSL is synthetic adrenocortical hormone which works as anti-inflammatory agent. Therapeutic efficacy was evaluated using X-ray, MRI, blood tests, DAS 28-CRP and by checking mouth-opening distance. The panoramic TMJ radiograph showed osteophysis, flattening, and osteosclerosis around the erosion of the left mandibular condyle **(Figure 3).**

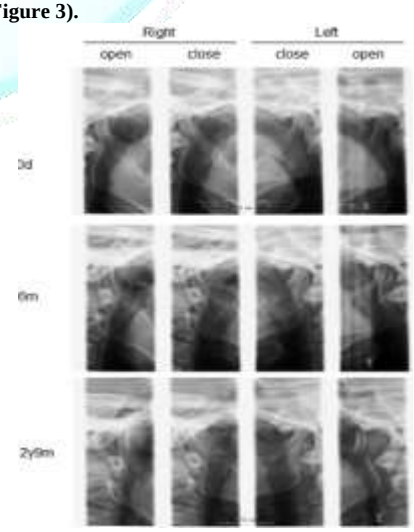

Figure 3: Panoramic TMJ radiograph at 0 days, 6 and 33 months after initial presentation.

In the T2-weighted MRI image, a low signal area (bone edema) was detected under the cortex of the left anterior mandibular condyle, indicating a progressing osteosclerosis. In the Proton-Density Fast Spin-Echo (PD FSE) image, the left anterior derangement of the joint disc was preceded, and the left mandibular cortical bone became thinner and there was progression of osteophytosis after 3 years. In the right TMJ, there was no change in TMJ disc derangement with reduction and no significant change in the condyle **(Figure 4).**

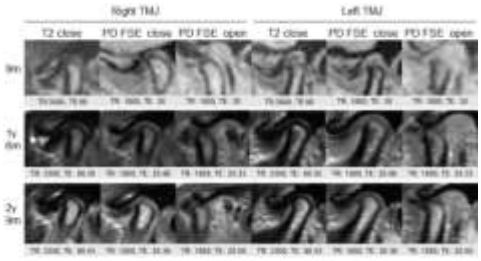

Figure 4: MRI of the right and left temporomandibular joints at 9, 18, and 33 months.

Blood tests were done to check for certain markers of RA such as Rheumatoid Factor (RF), Hemolytic Complement Activity (HCA) (CH50), Matrix Metalloproteinase 3 (MMP-3), Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). During treatment with SASP and ETN, CH50 was within the normal range. RF was within the normal range while ETN was used. MMP-3 was high, but values decreased while treatment with ETN continued. ESR was high before ETN administration and during ETN discontinuation. She needed to discontinue the ETN because of pregnancy, as a result, causing the concentrations of RA markers to increase. MMP-3 might be raised by PSL. DAS 28-CRP was 3.01 at 2 months, 1.73 at 11 months, 1.27 at 12 months, 3.14 at 31 months, and after the first visit **(Figure 5).**

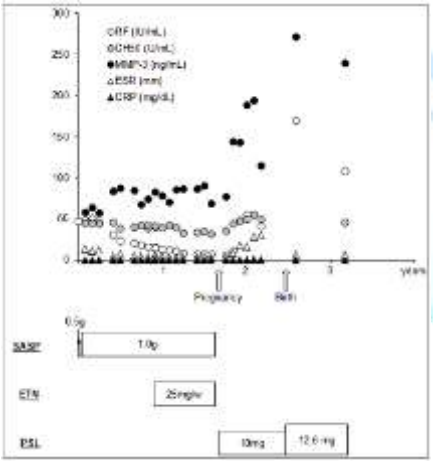

Figure 5: Time series data for blood test markers for Rheumatoid Arthritis (RA) and drugs used for RA. rheumatoid factor (RF); CH50, Hemolytic Complement Activity (HCA); Matrix Metalloproteinase 3 (MMP-3); Erythrocyte Sedimentation Rate (ESR); C-Reactive Protein (CRP); Salazosulfapyridine (SASP); Etanercept (ETN); Prednisolone (PSL).

When ETN was started, the DAS 28-CRP value decreased. The mouth-opening distance increased after the start of ETN administration. Even after discontinuation, the patient was able to maintain the opening distance to some extent because she continued visiting the hospital and doing jaw-training. Numeric rating scale (NRS) was showed low score during ETN administration **(Figure 6,7A,7B).**

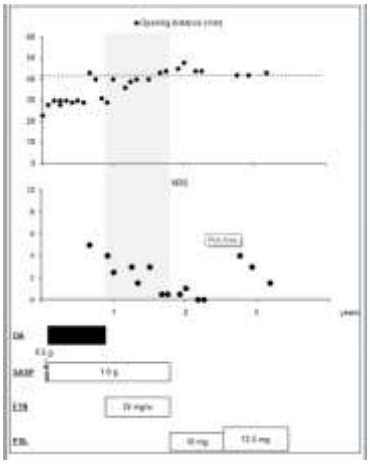

Figure 6: Time series data for mouth-opening distance, numeric rating scale, temporomandibular disorder treatment and drugs used for Rheumatoid Arthritis (RA). Numeric Rating Scale (NRS); Oral Appliance (OA); Salazosulfapyridine (SASP); Etanercept (ETN); prednisolone (PSL).

Figure 7A: Facial photo with mouth closed (left) and opened (right) at 2 years.

Figure 7B: Oral photos at 2 years.

Discussion

Newly revised RA classification criteria by the EULAR in 2010 increased the diagnostic sensitivity in the early stages of RA. With the increase in the number of patients diagnosed as having RA due to the less strict diagnostic criteria, the number of patients with RA in the TMJ is expected to increase. According to a report by Tabeling, et al. [8], the TMJ is affected in approximately 50% of cases of RA. In addition, as mentioned above, it was reported that some temporomandibular joint symptoms were found in 70% of RA patients [3].

Further, Marini, et al. [9] reported that erosive changes in the TMJ were detected on X-ray in two-thirds of patients. In this case, fortunately we were able to diagnose the patient as having RA early in the disease course by focusing on the findings that the initial symptom developed in the TMJ, that joint symptoms also developed in the hands and feet, and that these symptoms were worse in the morning, among others. In cooperation with rheumatologists in our hospital, the patient was treated with ETN early and were able to alleviate symptoms in joints of the whole body, including the TMJ.

The present case suggests the effectiveness of a biological product (ETN, a TNFα inhibitor) in controlling RA of the TMJ in its early stage, and confirmed the necessity of continuous treatment. Etanercept

(ETN) is a glycoprotein consisting of the Fc region of human IgG1 and the 75-kDa human tumor necrosis factor receptor 2. It exerts an anti-rheumatic and anti-inflammatory action through a mechanism in which the human TNF soluble receptor region works as a decoy to capture excessively produced TNFα and TNFβ and inhibits their binding to receptors on the cell surface. After the treatment of the ETN, the patient became pregnant and gave birth, therefore, necessitated to stop the ETN treatment during this time. After that, DAS28-CRP score was elevated, demonstrating a relapse of disease activity. Blood tests also showed increasing the levels of RF, MMP-3, CH50 and ESR.

Exacerbation of some TMJ symptoms, such as increased pain, were also observed accompanied with the increased systemic disease activity. In contrast, the alleviation of TMJ symptoms was achieved when the ETN treatment was resumed. Recently, usage of biological products for RA has increased, and many papers have reported their strong therapeutic effect. For example in oral diseases, ETN improves periodontal conditions by reducing periodontal inflammation. However, there are only a few papers on the use of biological products for TMJ symptoms. It has been suggested that biological products can be effective for temporomandibular joint symptoms as well as joints in the whole body, although this requires confirmation in a larger number of patients [10-12].

Considering the mouth-opening distance, an indicator of TMJ dysfunction, the combination of jaw-training and using OA are thought to have been effective. Generally, exercise therapy at the initial stage of RA is important to prevent loss of normal function in joints due to the rapid onset of deterioration. Similarly, we think that mouth-opening distance was maintained by the jaw-training and that the use of OA stabilized occlusion helped to alleviate the pain by reducing external forces on the joint surfaces.

Moreover, with the treatment of ETN, the TMJs became stabilized by inhibiting inflammation. No therapy for TMJ symptoms in RA patients has yet been established. In our experience of one case, there is little evidence; however, we believe that the usage of biological products and jaw-training with an OA may be effective for RA with TMD. In the future, further consideration including many cases will be needed.

Patient consent

Informed consent was gained for inclusion of a de-identified photograph.

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