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Case Report Open Access

Dramatic Effect of Tofacitinib on TNF-Inhibitor Resistant Synovitis: A Case Report

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Abstract

A 58-year-old woman with a 2.5-year history of rheumatoid arthritis showed a pain, severe swelling, and a decreased range of motion of left knee joint. Medical therapy with 8 mg per week of oral methotrexate and 1 mg per day of tacrolimus in combination with 40 mg per 2 weeks of adalimumab failed to control the disease activity. Administration of tofacitinib achieved the successful disease control, and MRI taken 5 months after the initiation of tofacitinib showed the disappearance of synovial mass within the knee joint and the bone marrow oedema and marked reduction of the popliteal cyst. The use of tofacitinib for inadequate response to the first TNF inhibitor as a third-line DMARD showed dramatic effect on severe synovitis, and the patient could avoid the surgical intervention.

Keywords: Rheumatoid arthritis; Tofacitinib; TNF-IR; Synovitis; MRI

Introduction

Rheumatoid arthritis (RA) is the most common autoimmune disorder characterized by inflammatory synovitis and progressive joint destruction [1]. Recent introduction of biologic therapeutics targeting key pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) have achieved marked improvement of disease control and better functional outcome in RA patients. However, about 20-40% of patients show inadequate response or intolerance to the TNF-inhibitors [2], and require additional managements. The pathophysiology that drives inflammation may be different among this subgroup of patients, and the targeting therapy other than TNF might be preferable. The 2015 American College of Rheumatology recommendations for the treatment of Established RA suggested the use of non-TNF biologic such as tocilizumab or abatacept for patients with a single TNF inhibitor (TNFi) failure over another TNFi and tofacitinib with or without methotrexate (MTX) [3]. Surgical treatment such as arthroscopic synovectomy for limited number of joint synovitis resistant to the pharmacologic treatment may be another option by reducing the volume of synovial membrane and improve the joint function [4]. The current case report describes the dramatic effect of tofacitinib on the knee joint synovitis of a patient with inadequate response to adalimumab as a first biologic, who could avoid the surgical synovectomy.

Case report

The patient, a 58-year-old woman with a 2.5-year history of RA presented to our outpatient clinic at the department of orthopaedic surgery complaining of pain, severe swelling, and a decreased range of motion (ROM; 35 degrees in flexion) of the left knee joint. Medical therapy with 8 mg per week of oral MTX and 1 mg/day of tacrolimus in combination with 40 mg per 2weeks of adalimumab failed to control the disease activity (Figure 1).

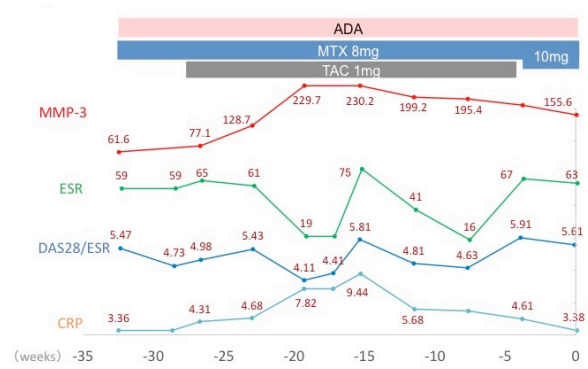

Figure 1: The change of MMP-3 (ng/mL), erythrocyte segmentation ratio (ESR) at 1 hour (mm), DAS28/ESR, and CRP (mg/dL) before administration of tofacitinib (week 0). ADA: adalimumab; MTX: methotrexate; TAC: tacrolimus.

The radiographic examination showed Larsen grade 0 joint appearance without joint space narrowing and bone erosion (Figure 2A),

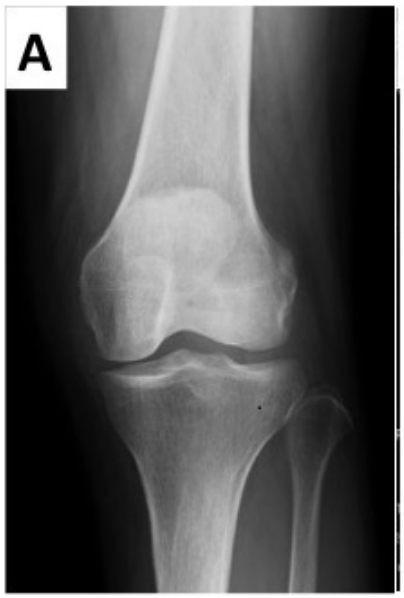

Figure 2: Radiograph (A) and MR image of the left knee joint before administration of tofacitinib. Arrow indicates popliteal cyst.

but MRI showed severe synovial proliferation at the knee joint (Figure 2).

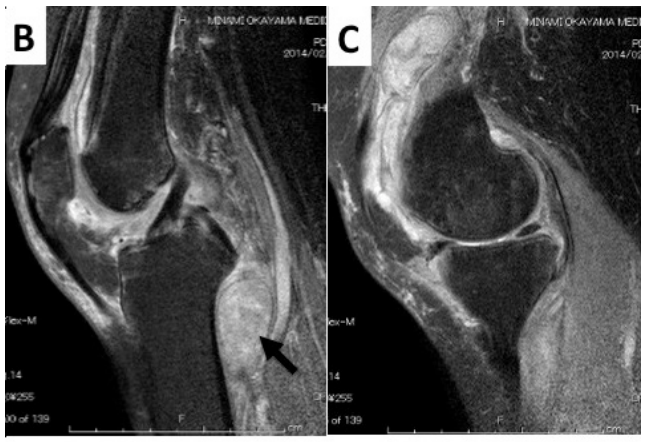

Figure 2: Radiograph (B,C) and MR image of the left knee joint before administration of tofacitinib. Arrow indicates popliteal cyst.

Although we suggested arthroscopic synovectomy, the patient chose treatment with tofacitinib. Before administration of tofacitinib, tacrolimus was discontinued and does of MTX was increased to 10 mg/week for 4 weeks. She still had high disease activity with a DAS28-ESR of 5.61, and the levels of CRP and serum MMP-3 were 3.38 mg/dL and 155 ng/mL, respectively. Then 5 mg/day of tofacitinib was administrated for 4 weeks together with 4 mg/W of MTX. The dose of tofacitinib was then increased to 10 mg/day and MTX was reduced to 2mg/week. The DAS28-ESR was improved to 3.8, as well as the levels of CRP and serum MMP-3 to 0.34 mg/dL and 36.8 ng/mL, respectively, at 15 weeks (Figure 3),

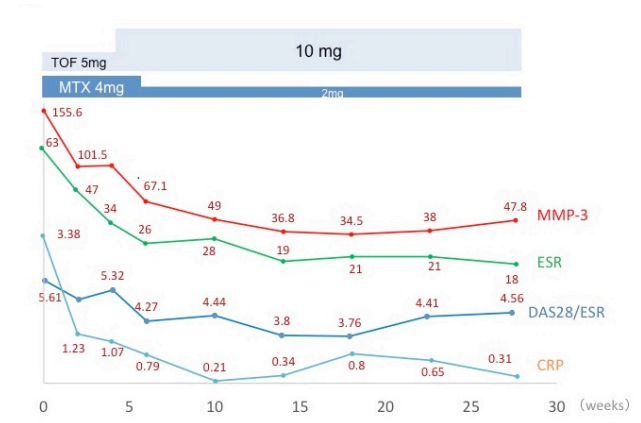

Figure 3: The change of MMP-3 (ng/mL), erythrocyte segmentation ratio (ESR) at 1 hour (mm), DAS28/ESR, and CRP (mg/dL) after administration of tofacitinib (week 0). TOF: tofacitinib; MTX: methotrexate.

with improvement of knee joint range of motion. MRI taken 5 months after the initiation of tofacitinib showed that the synovial mass within the knee joint and the bone marrow oedema disappeared and the size of the popliteal cyst was markedly reduced (Figure 4).

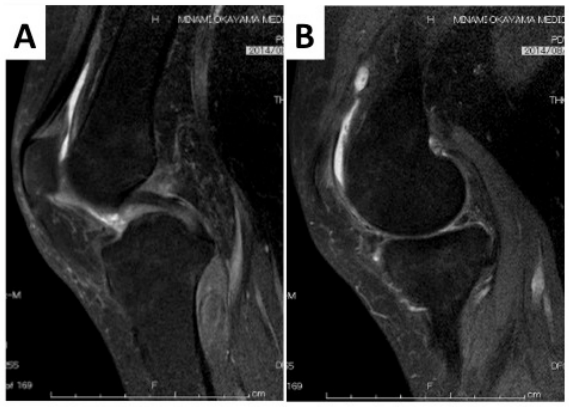

Figure 4: MR image of the left knee joint five months after administration of tofacitinib showing the marked reduction of synovial inflammation and popliteal cyst. Image (A) and (B) correspond to the image (B) and (C) in Figure 1, respectively.

as a result, the patient was able to avoid surgery and regained a pain-free knee joint with a normal ROM at present.

Discussion

Surgical synovectomy has been indicated for the isolated synovitis that is resistant to the medical therapy, and can achieve significant improvement of joint function with pain relief. Along with volume reduction of synovial membrane, the amount of inflammatory cytokines might be also reduced, thus promoting the efficacy of monoclonal antibodies against targeted molecules [4]. However,

surgery itself is invasive, and it has been suggested that the recurrence of synovitis and progression of joint destruction may be seen [5] without effective pharmacological disease control after the surgery.

Tofacitinib is the first oral Janus kinase (JAK) inhibitor for the treatment of RA [6]. Tofacitinib has been demonstrated to show consistent efficacy for inadequate response (IR) and intolerance to disease-modifying antirheumatic drugs (DMARDs) including MTX [7,8] or TNFi [6,9]. As for safety profile, tofacitinib has been reported to be associated with infections and malignancies and elevations in serum creatinine and lipids [7], but more recent studies demonstrated the consistent and manageable safety in RA patients [10-12].

For patients with IR to the first TNFi, the number of treatment options has been increased with the introduction of non-TNF biologics such as tocilizumab or abatacept [2]. However, the optimal treatment strategies that include the use of tofacitinib have yet to be established for patients with TNF-IR, because of the lack of randomized, prospective, head-to-head clinical trial. We learned from the current case about the usefulness of tofacitinib that can be used as a third-line DMARD in the recent pharmacologic strategy for RA.

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