Refractory Psoriatic Arthritis Responding to an Increased Dose of the Anti-TNF Monoclonal Antibody Adalimumab

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Abstract
Psoriatic arthritis (PsA) is a seronegative and chronic inflammatory arthritis that is associated with psoriasis. The standard dose of the anti-TNF monoclonal antibody adalimumab (ADA, 40 mg/2 weeks) has clinical indication for PsA, but there has been no clinical trial showing the efficacy and safety of treatment with an increased dose of ADA (80 mg/2 weeks) for PsA. Here we report the case of PsA that relapsed after discontinuation of treatment with ADA, was refractory to re-treatment with ADA (40 mg/2 weeks) and methotrexate (MTX), and was successfully treated with an increased dose of ADA (80 mg/2 weeks) with MTX. A 46-year-old man who had been diagnosed as having psoriasis at the age of 40 years and had been treated with topical corticosteroids was admitted to our hospital due to arthralgia and back pain with deterioration of psoriasis. He was diagnosed with psoriatic arthritis and was treated with 40 mg/2 weeks of ADA with MTX. After the start of treatment, he achieved remission, but he suddenly discontinued his treatment with ADA and MTX. Six months after the discontinuation of treatment, his psoriasis and arthritis deteriorated. Re-treatment with 40 mg/2 weeks of ADA with MTX did not improve his symptoms, and he was treated with an increased dose of ADA (80 mg/2 weeks) with MTX, leading to re-remission. Our case suggests that dose escalation of ADA with MTX is a potential treatment for PsA that has relapsed after discontinuation of treatment with ADA and is refractory to re-treatment with ADA (40 mg/2 weeks) and MTX as secondary failure.

Introduction
Psoriatic arthritis (PsA) is chronic inflammatory arthritis that is associated with psoriasis, and about 20 to 30% of psoriatic patients develop arthritis within several years of the primary diagnosis of psoriasis [1,2]. The etiology of the disease is unclear, though genetic associations have been identified. PsA is usually seronegative, and serological characteristics of PsA are distinct from those of rheumatoid arthritis (RA). More than half of PsA patients exhibit progressive and erosive arthritis that is associated with a reduction of the quality of life, and bony destructive changes usually appear several months after the onset of arthritis [3,4].

Adalimumab (ADA) is the first fully human, recombinant immunoglobulin G1 (IgG1) anti-TNF monoclonal antibody [5]. It has been reported that treatment of PsA with the standard dose of ADA (40 mg/2 weeks) improves symptoms and physical function and inhibits the progression of joint damage and that 80 mg/2 weeks of ADA monotherapy without disease-modifying antirheumatic drugs (DMARDs) also has clinical indication for refractory PsA in Japan but not in other countries. However, this indication was based on the clinical study in patients with moderate to severe psoriasis in Japan (M04-702), and there has been no clinical trial showing the efficacy and safety of treatment with an increased dose of ADA (80 mg/2 weeks) for PsA.

Here we report the case of PsA that relapsed after discontinuation of treatment with ADA, was refractory to re-treatment with ADA (40 mg/2 weeks) and methotrexate (MTX), and was successfully treated with an increased dose of ADA (80 mg/2 weeks) with MTX.
**Case presentation**

A 46-year-old man who had been diagnosed as having psoriasis at the age of 40 years and had been treated with topical corticosteroids was admitted to our hospital due to arthralgia and back pain with deterioration of psoriasis. On admission, he showed swollen joints on his shoulders, left elbow, left hand, knees and bilateral maniplhalanx suggesting dactylitis, and the Disease Activity Score 28-joint count based on C-reactive protein (DAS28-CRP) was 5.5. Laboratory data showed an elevated white blood cell (WBC) level (10,970 /μL; reference range, 3300–8600 /μL) and an elevated C-reactive protein (CRP) level (11.22 mg/dL; reference range, 0.00-0.15 mg/dL) (Table 1). A pelvic X-ray showed bilateral osteosclerosis in the sacroiliac joint, and magnetic resonance imaging (MRI) of the pelvis showed bilateral osteosclerosis with subchondral bone marrow edema in the left sacroiliac joint, suggesting sacroilitis. Bone scintigraphy showed positive uptake in the knees, shoulders, sternoclavicular joint and sacroiliac joint. Chest computed tomography (CT) revealed no evidence of infectious pneumonia or aggravation of interstitial lung disease. He was diagnosed with PsA and was treated with 10 mg/week of MTX in combination with 40 mg/2 weeks of ADA, but the dose of MTX was reduced to 4 mg/week due to liver injury. Two months after the start of treatment, he achieved remission with improvement of swollen joints and psoriasis and reduction of DAS28-CRP to 1.23. Four months after the start of treatment, he suddenly discontinued treatment with MTX and ADA. Six months after the discontinuation of treatment, he presented to our hospital due to deterioration of arthralgia and psoriasis with elevated serum level of CRP (14.71 mg/dL) and elevated DAS28-CRP (6.4). Despite restarting treatment with 6 mg/week of MTX in combination with 40 mg/2 weeks of ADA for 2 months, his swollen joints and psoriasis did not improve, that is, secondary failure of re-induction of remission. Since laboratory data did not show any sign of adverse drug reaction, he was re-treated with an increased dose of ADA (80 mg/2 weeks) in the presence of MTX, which resulted in re-remission with disappearance of the psoriasis and swollen joints and reduction of DAS28-CRP (1.24) 2 months after the start of treatment with ADA at 80 mg/2 weeks. He has maintained remission for 16 months without relapse.

| Haematology | Blood chemistry | Serological test | Immunological test |
|-------------|-----------------|------------------|--------------------|
| WBC 10970 /μL | TP 8.2 g/dL     | CRP 11.22 mg/dL  | RF 7.9 IU/mL       |
| Neutro. 62.00% | Alb 3.5 g/dL    | ESR 100 mm/h     | ANA <0.08 Ratio    |
| Lymph. 26.00%  | T. Bil 0.34 mg/dL | IgG 2034.9 mg/dL | SS-A <0.50 U/mL    |
| Mono. 7.00%    | AST 12 U/L      | IgA 699.7 mg/dL  | SS-B <0.50 U/mL    |
| Eosino. 2.00%  | ALT 16 U/L      | IgM 77.8 mg/dL   | MPO-ANCA <0.50 IU/mL|
| RBC 5.03×10⁶ /μL | CK 47 U/L     | C3 180.2 mg/dL   | PR3-ANCA <0.50 IU/mL|
| Hb 14.0 g/dL | ALP 298 U/L    | C4 44.7 mg/dL   | ds-DNA 0.54 IU/mL  |
| Ht 44.90% | γGTP 51 U/L     | CH50 58 U/mL     | RNP 1.66 U/mL      |
| MCV 89.1 fl | ChE 328 U/L    |                 |                   |
| MCH 27.7 pg | LDH 132 U/L    |                 |                   |
| MCHC 31.1 g/dL | AMY 91 U/L   |                 |                   |
| Plt 66.0×10⁴ /μL | BUN 19.7 mg/dL |                 |                   |
|              | Cr 0.63 mg/dL  |                 |                   |
|              | UA 5.0 mg/dL   |                 |                   |
|              | Na 135 mmol/L  |                 |                   |
|              | K 4.8 mmol/L   |                 |                   |
|              | Cl 100 mmol/L  |                 |                   |
|              | Ca 9.4 mg/dL   |                 |                   |
|              | Ferritin 604 ng/mL |           |                   |
|              | HbA1c 10.50%   |                 |                   |

**Table 1:** Laboratory data for the present case on admission.
Discussion

ADA has been implicated in several inflammatory bone diseases including RA, PsA, and ankylosing spondylitis (AS). TNF is a key player in the pathogenesis of PsA as well as RA, though the clinical features of PsA including skin lesions, enthesitis and dactylitis are different from those of RA. The bony destruction pattern observed in PsA is also different from that in RA. Combined erosion and ectopic new bone formation called pencil-in-cap in the distal interphalangeal (DIP) joint is occasionally observed in RA. It has been reported that the switch of bone dynamics in patients with RA and AS that shows ectopic new bone formation [6]. A low concentration of TNF induces osteoinductive Wnt proteins, leading to osteoblast-mediated bone formation in AS, while a high concentration of TNF induces inflammatory cytokines, leading to osteoclast-mediated bone resorption in RA. Pencil-in-cap appearance with erosion and bone formation in PsA may be caused by activation of both osteoclasts and osteoblasts, which are regulated in a manner similar to that of both RA and AS.

The ARMADA (Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab) trial showed a significant improvement in disease activity in patients with RA who were treated with MTX in combination with ADA (20 mg, 40 mg, or 80 mg/2 weeks) compared with the disease activity in patients who received MTX alone [7]. The ADEPT (Adalimumab Effectiveness in Psoriatic Arthritis Trial) study showed significant efficacy of ADA (40 mg/2 weeks) comparing to a placebo in patients with severe PsA: ACR 20 (57% vs 15%), PsARC (60% vs 23%) and PASI 75 (59% vs 1%) [2, 4]. Dose escalation of ADA from 40 to 80 mg/2 weeks in the presence of MTX did not show a clinical benefit in patients with RA in the ARMADA trial [7], while there has been no clinical trial showing the efficacy and safety of treatment of PsA with an increased dose of ADA (80 mg/2 weeks) regardless of the presence or absence of MTX. Additionally, in contrast to the additive effect of MTX on ADA in patients with RA, addition of MTX did not change the efficacy of ADA in patients with PsA in the ADEPT study [2, 4], indicating that the pathogenesis and therapeutic strategies in RA may be different from those in PsA. Nevertheless, it is stated in the drug package insert of ADA that 80 mg/2 weeks of ADA in the presence of DMARDs including MTX is not recommended for RA or for PsA in Japan, leading to the clinical indication of an increased dose of ADA monotherapy for refractory PsA. Additionally, this indication was based on the clinical study in patients with moderate to severe psoriasis (M04-702), but not with PsA in Japan. A previous case report therefore focused on the effectiveness of an increased dose of ADA monotherapy without MTX for PsA in which remission induction with the standard dose of ADA failed [8].

In contrast to the previously described case, we found in the present case that an increased dose of ADA in the presence of MTX was effective and safe for PsA that had relapsed after discontinuation of treatment with ADA and was refractory to retreatment with ADA and MTX. A recent study showed that the appearance of antidrug antibodies against ADA had an inverse relation to the serum concentration of ADA in patients with RA and that 22% of RA patients receiving ADA developed detectable antidrug antibodies during a follow-up period of 52 weeks [9]. Although we did not measure antidrug antibodies in our case, dose escalation of ADA from 40 to 80 mg/2 weeks with MTX may be effective for PsA that has relapsed after stopping treatment with ADA, which may induce the production of antidrug antibodies. Further trials are required to show the clinical efficacy and safety of treatment with an increased dose of ADA regardless of the presence or absence of DMARDs for PsA.

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