

CASE REPORT

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Adalimumab Monotherapy in a Patient with Psoriatic Arthritis Associated with Chronic Renal Failure on Hemodialysis: A Case Report and Literature Review

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Abstract: We report a patient with psoriatic arthritis (PsA) who was successfully treated with adalimumab even while under hemodialysis therapy for associated chronic renal failure. Flow cytometry of circulating lymphocytes revealed an obvious decrease in both Th1 and Th17 cells after starting adalimumab. The latter returned to the pretreatment level in the course of adalimumab therapy, while the former did not. Adalimumab is a potent therapeutic option for PsA patients with chronic renal failure on hemodialysis, and Th1 in peripheral blood may reflect the disease activity.

Keywords: adalimumab, psoriatic arthritis, hemodialysis, Th1, Th17

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Introduction

Psoriasis is a chronic inflammatory skin disease characterized clinically by red scaly patches developing in any part of the body with a relapse-remitting course. Systemic arthritis complicates psoriasis in approximately 20% of the patients,¹ and its clinical picture resembles that of rheumatoid arthritis with regard to therapeutic efficacy of the monoclonal anti-tumor necrosis factor (TNF)- α antibody, such as infliximab and adalimumab. Several recent reports have demonstrated that T-helper 1 cells (Th1), T-helper 17 cells (Th17) and regulatory T cells (Treg) may play a central role in the pathogenesis of psoriatic arthritis (PsA) via interaction with dendritic cells, leading to accelerated production of TNF.^{2,3} Here, we report a patient with PsA associated with chronic renal failure on hemodialysis who was successfully treated with adalimumab alone. Flow cytometry showed a persistent decrease in Th1 cells after starting adalimumab, and we postulate that this circulating lymphocyte subpopulation may be useful as a therapeutic marker of PsA.

Case Report

A 57-year-old man with a 9-year history of hemodialysis for chronic renal failure due to glomerulonephritis became aware of arthralgia in multiple joints with no precipitating cause. He was treated with oral prednisolone at a dose of 5 to 7.5 mg daily in a neighboring hospital, but systemic arthralgia worsened gradually. When he was referred to our hospital, physical examination showed swelling and tenderness in bilateral proximal interphalangeal (PIP) joints, wrists, knees, ankles and metatarsophalangeal joints with no significant skin lesions. Laboratory tests demonstrated an increase in inflammatory reactions, such as C-reactive protein (CRP) (1.28 mg/dL, normal <0.1 mg/dL) and renal dysfunction (creatinine 4.28 mg/dL, normal 0.6–1.0 mg/dL; blood urea nitrogen 78.5 mg/dL, normal 8–20 mg/dL) but no positive results in autoantibodies, including rheumatoid factor and the anti-cyclic citrullinated peptide and anti-nuclear antibodies. The X-ray showed mild bone erosions on PIP joints. The disease activity score including a 28-joint count (DAS28)-CRP calculated according to the approved formula (<http://www.das-score.nl/>) was 3.79. Salazosulfapyridine at 1000 mg daily could not sufficiently relieve his arthralgia.

Approximately 10 months later he noticed eruptions on his head, elbows, fingers and knees with hyperkeratosis and discoloration in his nails, which were clinically diagnosed as psoriasis by a dermatologist, in conjunction with worsening of his systemic arthritis and elevations of CRP (3.31 mg/dL) (Fig. 1). The psoriasis area and severity index (PASI) was relatively low (6.0), but DAS28-CRP indicated high disease activity of arthritis (6.88). Adalimumab was started at 80 mg initially, followed by 40 mg every other week. The patient showed dramatic improvement of his arthritis as well as psoriasis, and DAS28-CRP and PASI decreased to 2.41 and 2.8, respectively, 2 weeks after starting adalimumab (Fig. 2). On flow cytometry before treatment CD4⁺ interferon- γ ⁺ (Th1) and CD4⁺ interleukin-17⁺ (Th17) cells in peripheral blood were higher than those of age-matched healthy controls, but CD4⁺CD25⁺FOXP-3⁺ cells (Treg) showed no obvious increase. All of these lymphocyte subpopulations were decreased eight weeks after starting adalimumab compared with before (Fig. 2). CD4⁺ interleukin-4⁺ cells (T-helper 2) showed no significant change before and after treatment. Twelve weeks after starting adalimumab, CD4⁺ interleukin-17⁺ and CD4⁺CD25⁺FOXP-3⁺ cells returned to the pretreatment level but CD4⁺ interferon- γ ⁺ cells remained at low levels. He has since been in good general health



Figure 1. The patient showed psoriatic eruptions on the surface of hemodialysis shunt (A) and on the left knee (B) with hyperkeratosis and discoloration in fingernails (C).

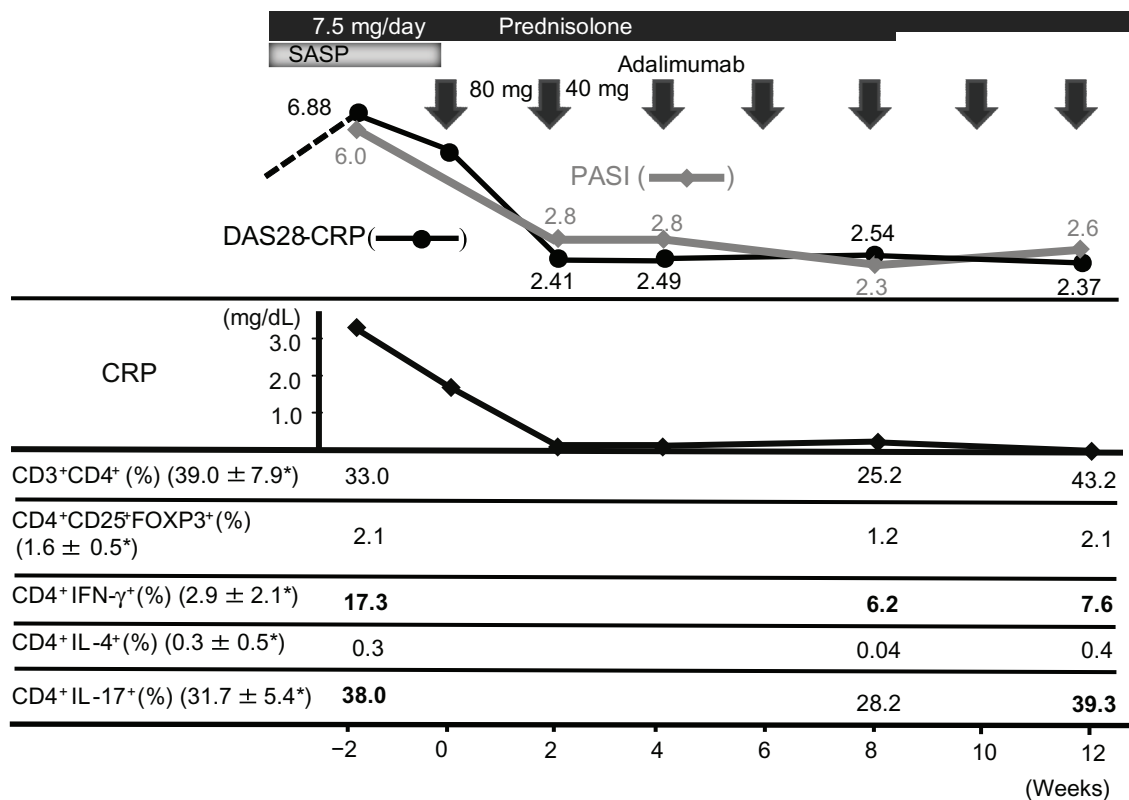


Figure 2. The clinical profile of the patient.

Note: *Mean \pm 2SD in 10 age-matched healthy subjects.

Abbreviations: CRP, C-reactive protein; DAS28, disease activity score including a 28-joint count; IFN, interferon; IL, interleukin; PASI, psoriasis area and severity index; SASP, salazosulfapyridine.

with no arthralgia or adverse events under regular administration of adalimumab.

Discussion

The present patient was diagnosed as having PsA based on polyarthritis with skin and nail lesions characteristic of psoriasis. In approximately 19% of PsA polyarthritis has been reported to precede psoriasis, as seen in the present patient.⁴ Methotrexate and cyclosporine A are usually potent therapeutic options for PsA, but these drugs were inadequate in the present patient because of chronic renal failure requiring hemodialysis.⁵ Biologics are the next choice. Several recent reports have demonstrated that early use of biologics can ameliorate polyarthralgia and skin lesions in rheumatic disorders, including PsA, associated with chronic renal failure on hemodialysis (Table 1).⁵⁻¹² Biologics targeting TNF are most frequently used in this situation, and among them etanercept has been reported to show pharmacokinetics similar to those in healthy subjects even under chronic renal failure on hemodialysis.¹³ However, the use of etanercept is

not allowed in PsA in Japan. In the present patient, therefore, we decided to employ adalimumab, which is a human anti-TNF- α monoclonal antibody usable in PsA without coadministrations of methotrexate. The usual dose of adalimumab is 40 mg, but 80 mg was selected as an initial dose in the present patient because of severe systemic arthritis.¹⁴ Soon after starting this drug both polyarthritides and psoriasis improved in parallel with a decrease in inflammatory reactions. The patient has so far shown no serious adverse events ascribable to adalimumab.

In the present patient we serially analyzed phenotypes of peripheral blood lymphocytes using flow cytometry. Th1 and Th17 cells showed significantly higher levels before treatment compared with those of age-matched healthy controls as described in the previous report from another institute,² but Treg cells did not. These 3 lymphocyte subpopulations manifestly decreased 8 weeks after starting adalimumab. Th17 and Treg cells returned to the pretreatment level 12 weeks after starting adalimumab, while Th1 cells remained at low levels in conjunction with

Table 1. Reported cases with biologics therapy in rheumatic diseases associated with renal failure.

Author	Onset age/sex	Rheumatic diseases	Cause of renal failure	Duration of HD or PD on starting biologics therapy	Biologics used	Outcome of rheumatic diseases	Adverse events
Yee ⁶	72/F	Sarcoidosis	Drug-induced acute tubular necrosis	Several weeks	Infliximab	Improved	Hypercoagulation
Singh ⁷	60/F	RA	Hypertensive nephrosclerosis	Several months	Infliximab	Improved	None
Hammoudeh ⁸	45/F	RA	Chronic glomerulonephritis and chronic rejection of transplanted kidney	9 years	Infliximab	Improved	Transient itching
Sugioka ⁹	64/F	RA	Chronic glomerulonephritis	2 years	Etanercept	Improved	None
Cassano ¹⁰	69/M	Psoriasis	Chronic glomerulonephritis	9 years	Etanercept	Improved	None
Kobak ¹¹	65/M	AS	Autosomal polycystic kidney	6 years	Adalimumab	Improved	None
Saougou ⁵	52/M	PsA	ND	2 years	Infliximab	Improved	None
Iwamoto ¹²	64/M	RA	Chronic glomerulonephritis	15 years	Tocilizumab	Improved	None
Present patient	58/M	PsA	Drug-induced renal failure	11 years	Adalimumab	Improved	None

Abbreviations: AS, ankylosing spondylitis; HD, hemodialysis; ND, not described; PD, peritoneal dialysis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

the suppressed activity of PsA. The decreases in Th1, Th17 and Treg cells after treatment are ascribable to 3 possible mechanisms. The first is a direct cytotoxic effect of adalimumab. This drug can react with TNF- α in peripheral blood but also with that expressed on immune competent cells, including T lymphocytes.¹⁵ The interaction between TNF- α on the cell surface and adalimumab may have produced cytotoxicity, resulting in a rapid elimination of Th1, Th17 and Treg cells. The second possible mechanism is anti-TNF-mediated induction or recovery of cell populations capable of regulating Th1 and Th17 cells.¹⁶ Treg cells are suitable candidates, but in the present patient this subpopulation was simultaneously decreased 8 weeks after starting adalimumab. The third possible mechanism is inhibition of circulating TNF- α , which has multipotentials on immune systems. As TNF- α can promote differentiation and maturation of T cells,^{2,16} adalimumab-induced reduction of this cytokine in peripheral blood may have caused alterations of T-lymphocyte subpopulations as seen in the present patient. The reincreases in Th17 and Treg cells 12 weeks after starting treatment are probably due to rapid differentiation or mobilization into peripheral blood via some other stimulating mediators, such as interleukin-2 and transforming growth factor- β ¹⁷⁻¹⁹ although the precise mechanisms are unclear. Chronic renal failure itself also has a positive effect on Th17 cells irrespective of maintenance hemodialysis.²⁰ Considering that Th1 cells were the only lymphocytes showing obvious change persistently after starting adalimumab in the present patient, this subpopulation may be able to more sensitively reflect disease activity of PsA than Th17 and Treg.

In conclusion, adalimumab monotherapy is a potent therapeutic option in patients with PsA with regard to clinical efficacy and safety even under hemodialysis for associated chronic renal failure. Further studies in a set of patients are necessary in order to clarify whether or not Th1 cells are a useful clinical marker indicating disease activity of PsA.

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Disclosures

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