

## A Case of Etanercept Treatment in a Patient with Ankylosing Spondylitis on Peritoneal Dialysis

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Treatments for patient with ankylosing spondylitis (AS) include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) and anti-tumor necrosis factor-alpha (TNF  $\alpha$ ) agents. However, owing to the well-known nephrotoxicity of NSAIDs and some DMARDs, the use of these drugs is limited in AS patients with renal insufficiency. As the pharmacokinetics and metabolism of anti-TNF  $\alpha$  agents in patients of end stage renal disease, especially those receiving peritoneal di-

alysis (PD), have not been investigated well, little is known about treating them with anti-TNF  $\alpha$  agents. We described the safety and efficacy of etanercept, a soluble fusion protein comprising the TNF receptor 2 in linkage with the Fc portion of immunoglobulin G, in a 40-year-old male AS patient receiving PD.

**Key Words.** Ankylosing spondylitis, End-stage renal disease, Peritoneal dialysis, Tumor necrosis factor-alpha

### Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis with the involvement of axial, peripheral and sacroiliac joints which can result in irreversible new bone formation and thus substantial functional disability. Enthesitis and extra-articular manifestations such as anterior uveitis may also be prominent features. In addition, renal involvement in patients with AS are not uncommon and secondary amyloidosis and IgA nephropathy are the most common glomerulonephritis associated with AS (1). In some patients, such renal abnormalities can lead to a progressive reduction in glomerular filtration rates eventually resulting in renal failure.

The primary goal of the management of patients with AS is to improve quality of life through control of inflammation and prevention of structural damage. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line drug treatments

for patients with AS and sulfasalazine (SSZ) may have some efficacy in patients with peripheral arthritis (2). In addition, anti-tumor necrosis factor-alpha (TNF  $\alpha$ ) agents recently have been recognized as a highly effective approach to treating AS patients with high disease activity despite conventional treatments (2). Owing to their potential for nephrotoxicity, the use of NSAIDs and SSZ are limited in AS patients with renal insufficiency. Meanwhile, the pharmacokinetics and metabolism of anti-TNF  $\alpha$  agents in patients with end-stage renal disease (ESRD), especially those receiving PD, has not been investigated, and very little is known about treating this population with anti-TNF  $\alpha$  agents. In this case report, the safety and efficacy of etanercept, a soluble fusion protein comprising the TNF receptor 2 in linkage with the Fc portion of immunoglobulin G, is described in a 40-year old male patient with AS who is receiving PD for renal replacement therapy.

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### Case Report

A 40-year old man diagnosed with AS and IgA nephropathy was referred to our clinic due to pain in the lumbosacral area, morning stiffness of 3~4 hour duration and arthralgias involving the left knee and right wrist despite the use of celecoxib, sulfasalazine and methylprednisolone for 4 years. Due to his progressive decline in kidney function, he was undergoing PD as a renal replacement therapy for the past 3 years. Physical examination revealed tenderness in the left knee, right wrist and both sacroiliac joints, left knee swelling and an AS posture. His swollen right fifth toe was consistent with dactylitis. Joint aspirates obtained from the left knee joint contained 18,690 white cells with 95% of neutrophils but no pathogenic organisms on culture or crystals on polarized light microscopy. Plain radiography showed loss of normal curvature and squaring of vertebral bodies in the cervical and lumbar spine and obliterations of both sacroiliac articulations. X-rays of the left knee and right wrist joints were unremarkable. Laboratory studies revealed a hemoglobin level of 8.8 mg/dL (normal 14.0~17.0 mg/dL), serum blood urea nitrogen (BUN) level of 71.2 mg/dL (normal 6~26 mg/dL), serum creatinine level of 11.8 mg/dL (normal 0.4~1.2 mg/dL), erythrocyte sedimentation rate (ESR) level of 120 mm/hr (normal 0~10 mg/dL), and a C-reactive protein (CRP) level of 19.4 mg/dL (normal 0~0.5 mg/dL). In addition, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 7.7, the Bath Ankylosing Spondylitis Disease Functional Index (BASFI) was 7.7, the Bath Ankylosing Spondylitis Disease Metrology Index (BASMI) was 5.6, the Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP) was 4.55, and ASDAS-ESR was 5.85, consistent with active AS.

**Table 1.** Clinical and laboratory findings in our patient with ankylosing spondylitis receiving peritoneal dialysis during etanercept treatment

	Baseline	3 month	9 month
BASDAI	7.7	4.6	1.2
BASFI	7.7	4.2	5.5
BASMI	5.6	3.8	3.6
ASDAS-CRP	4.55	4.03	1.8
ASDAS-ESR	5.85	4.57	2.96
CRP, mg/dL	19.4	9.1	2.3
ESR, mm/hr	120	95	59
BUN, mg/dL	71.2	66.5	74.8
Serum creatinine, mg/dL	11.8	12.2	12.1

BASDAI: bath ankylosing spondylitis disease activity index, BASFI: bath ankylosing spondylitis functional index, BASMI: bath ankylosing spondylitis metrology index, ASDAS: ankylosing spondylitis disease activity score, CRP: c-reactive protein, ESR: erythrocyte sedimentation rate, BUN: blood urea nitrogen.

In view of the patient's baseline information, etanercept treatment was discussed with the patient. PPD testing was negative and his chest radiograph revealed no active lung lesion. After obtaining his consent, etanercept at a 25 mg dose twice weekly subcutaneously was initiated. Three month after treatment with etanercept, all symptoms including inflammatory back pain, peripheral arthritis and dactylitis as well as laboratory parameters improved (Table 1). At the ninth month of treatment, significant improvement was noted in disease activity without any adverse effect on kidney function (Table 1). In addition, considering  $\Delta$ ASDAS-CRP and  $\Delta$ ASDAS-ESR were 2.75 and 2.89 respectively, the patient achieved "major improvement" on the basis of selected cut-offs for improvement score criteria by the Assessment of Spondyloarthritis international Society (ASAS). Furthermore, no obvious clinical side effects were observed in the patient during etanercept treatment.

### Discussion

Renal abnormalities are not uncommon in AS patients in the clinical setting. First, renal damage can occur owing to complications from long term NSAIDs. Second, various renal involvements related to AS are reported in approximately 10% (1). Secondary amyloidosis is the most common etiology followed by IgA nephropathy, but other forms of glomerulonephritis can occur. These conditions could lead to progressive decline of renal function and ESRD requiring renal replacement therapy. Lange et al. reported that 3.9% of AS patients suffered from chronic kidney disease (CKD) (3). Therefore, concomitant kidney disease and renal side effects of medications should be taken into account when managing AS patients.

However, treatment of AS patients with impaired renal function can be challenging due to nephrotoxicities associated NSAIDs and SSZ. Although continuous treatment with NSAIDs is recommended for persistently active AS patients, potential adverse effect of NSAID including acute deterioration of renal function, papillary necrosis, interstitial nephritis, edema and electrolyte imbalances may be increased in these patients (4). SSZ, which is also widely used for AS patients, is a salicylic acid derivative created by the covalent linkage of 5-amino-salicylic-acid (5-ASA) to sulfapyridine. Whereas sulfapyridine is considered to have anti-inflammatory properties in many rheumatic diseases, 5-ASA may cause nephropathy including glomerulonephritis, interstitial nephritis and acute renal failure similar to NSAIDs (5). Thus, the use of SSZ should be limited in patients with CKD.

Anti-TNF  $\alpha$  therapy can lead to clinical and laboratory improvements in AS patients with persistently high disease activity despite conventional treatments such as NSAIDs and

DMARDs, but the literature contains little information on the use of these agents in patients with CKD especially those receiving renal replacement therapy. Don et al. and colleagues reported that the pharmacokinetics of etanercept in subjects undergoing hemodialysis (HD) was similar to those with normal renal function (6). There was no significant difference in serum etanercept concentrations between the pre- and post-dialysis, thus HD did not affect the pharmacokinetics of etanercept. Also, no side effects were observed during the 3 month treatment period and subsequent 6 month follow-up. Hammoudeh reported on the infliximab treatment in a patient with rheumatoid arthritis (RA) on HD during 6 months (7). Sugioka et al. have administered etanercept to an active RA patient despite conventional treatment (8). During 12 weeks of treatment, significant improvements in disease activity were noted without any side effect. In addition, Saougou et al. and Shimojima et al. demonstrated that treating a psoriatic arthritis patient undergoing HD with infliximab and adalimumab respectively can be effective and safe (9,10). However, very little is known about the clinical application of anti-TNF  $\alpha$  agents in subjects on PD.

Our case report demonstrates the safety and efficacy of etanercept in a 40-year old male AS patient on PD. During 9 months of treatment, there were significant improvements in disease activity scores without any side effects. Kobak reported the successful treatment of adalimumab in a AS patient receiving PD for 12 weeks (11). However, the duration of treatment and follow-up was relatively short as compared with ours. In addition, we measured the patients ASDAS, a highly discriminatory tool for assessing disease activity in AS patients as compared with the conventional BASDAI. Thus, as far as we know, this is the first case report about the long term outcome of etanercept treatment for AS patient on PD, using a reliable and discriminative disease activity score.

### Summary

Our case suggests that etanercept can be an effective and safe approach to treat AS patients undergoing PD. However, further researches are required to assess the use of etanercept for patients with AS on PD.

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