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CASE REPORT

# Efficacy and safety of tacrolimus treatment for rheumatoid arthritis patients undergoing hemodialysis

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**Abstract** Rheumatoid arthritis (RA) is an autoimmune disorder characterized by progressive joint destruction that requires aggressive treatment using appropriate disease-modifying antirheumatic drugs (DMARDs). RA patients with renal failure, however, are intolerant to most DMARDs due to the potential toxicity. In Japan, tacrolimus was approved for the treatment of RA in 2005. Based on its pharmacokinetics, tacrolimus may be administered to the patients undergoing hemodialysis. We report two cases of RA patients on hemodialysis treated effectively and safely with tacrolimus.

**Keywords** Chronic renal failure · Hemodialysis · Pharmacokinetics · Rheumatoid arthritis · Tacrolimus

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by progressive joint destruction that requires early diagnosis and aggressive treatment using appropriate disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX). RA patients with renal failure, however, are intolerant to most DMARDs due to the potential toxicity.

MTX is cleared primarily by the kidney and has been associated with lethal complications in RA patients on hemodialysis even at very low doses [1]. Whether MTX can be administered to patients with renal failure undergoing hemodialysis has not been adequately addressed.

In Japan, several new drugs were approved for RA in recent years; leflunomide and infliximab in 2003, and etanercept and tacrolimus in 2005. It is considered that leflunomide and etanercept can be administered regardless of renal function based on their pharmacokinetics [2–4]. However, there are very few clinical reports demonstrating that these drugs are safe, well tolerated, and effective in patients with renal failure.

Tacrolimus is a strong immunosuppressive agent that selectively inhibits T cell activation. Its properties improve joint inflammation and retard bone destruction by suppressing the production of inflammatory cytokines [5]. It is used to prevent rejection of organ transplants and its pharmacokinetics has been comprehensively studied [6–9]. Tacrolimus is metabolized by the cytochrome P450-3A4 mainly in the liver, and less than 2% of the administered dose is excreted in urine as unchanged form. In addition, it is not removed in dialysis. Thus, tacrolimus may be administered to patients undergoing hemodialysis. Nevertheless, there have been no case reports about the effectiveness of tacrolimus for such RA patients. Here we report two cases of RA patients on hemodialysis treated effectively and safely with tacrolimus.

## Case reports

### Case 1

A 62-year-old woman with a 24-year history of RA (functional class II, radiographic stage IV) had complication of chronic renal failure due to IgA nephropathy and has been receiving hemodialysis therapy since 2000. She

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**Table 1** Characteristics of patients

| | Case 1 | Case 2 |
|---|---|---|
| Age (years), Sex | 62, Female | 62, Female |
| Disease duration of RA (years) | 24 | 32 |
| Past DMARDs therapy | SASP | GST, Buc, MTX, MZB |
| Complication | Chronic renal failure (IgA nephropathy) | Chronic renal failure (IgA nephropathy) |
| Functional class | II | II |
| Radiographic stage | IV | IV |
| Painful joints[a] | 6 | 5 |
| Swollen joints[b] | 15 | 4 |
| Patient assessment of pain[c] | 15 | 77 |
| Patient assessment of function (mHAQ) | 0.25 | 0.5 |
| Patient assessment of disease activity[d] | 16 | 64 |
| Physician assessment of disease activity[d] | 66 | 49 |
| CRP (mg/dl) | 5.08 | 0.266 |
| ESR (mm/h) | 75 | 10 |
| DAS28 (CRP) | 4.65 | 3.84 |
| Rheumatoid factor | Negative | Negative |
| Prednisolone dosage (mg/day) | None | 2.5 |

*RA* rheumatoid arthritis, *DMARDs* disease-modifying antirheumatic drugs, *SASP* sulfasalazine, *GST* glutathione S-transferase, *Buc* bucillamine, *MTX* methotrexate, *MZB* mizoribine, *mHAQ* modified Health Assessment Questionnaire, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* Disease Activity Score of 28 joints

[a] 68 joints were assessed for pain

[b] 66 joints were assessed for swelling

[c] Patient assessment of pain is based on visual analog scale (VAS), possible range of 0 (no pain) to 100 (pain as bad as it could be)

[d] Patient/physician assessment of disease activity is based on VAS, possible range of 0 (very well) to 100 (very poorly)

took one type of nonsteroidal anti-inflammatory drug (NSAIDs) for arthralgia and was started on sulfasalazine (SASP) in 2004 due to persistence of symptoms. As her arthritis was not improved, SASP was replaced with tacrolimus (1 mg/day) in May 2006. She had six painful joints and 15 swollen joints. On the visual analog scale (VAS) of 100 mm as a global assessment of pain, the patient indicated 16 mm. Her C-reactive protein (CRP) level was 5.08 mg/dl and erythrocyte sedimentation rate (ESR) was 75 mm/h. A disease activity score of 28 joints (DAS28) using the CRP level was 4.65, showing moderate activity. Here, instead of using ESR in the evaluation of DAS28, we used the CRP level, because she has concomitant renal anemia (hemoglobin 8.8 g/dl), which affects ESR. Rheumatoid factor was negative (Table 1). Liver function was normal (aspartate aminotransferase (AST) 11 U/l, alanine aminotransferase (ALT) 11 U/l, lactate dehydrogenase (LDH) 191 U/l, $\gamma$-glutamyl transpeptidase ($\gamma$-GTP) 33 U/l). Following 4 weeks of treatment with tacrolimus, the patient's swollen joint count decreased to seven, and CRP level normalized (0.262 mg/dl) (Fig. 1). At 8 weeks, the American College of Rheumatology (ACR) 20 response was achieved. The ACR 50 response was obtained 12 weeks later and ACR 70 response 28 weeks later. Thereafter, disease activity increased slightly for a short time due to overwork, but from 48 weeks ACR 20 or ACR 50 or ACR 70 has been achieved and DAS28 also has shown low activity (<3.20) (Table 2). Tacrolimus dose was gradually increased to 3 mg/day, but its blood concentration was within the margin of safety (0.94–2.1 ng/ml) (Fig. 1). The patient reports no side effects from tacrolimus and follows a good course.

## Case 2

A 62-year-old woman with a 32-year history of RA (functional class II, radiographic stage IV) had shown a poor response to DMARDs, such as glutathione S-transferase (GST), bucillamine (Buc), methotrexate (MTX) and mizoribine (MZB). She underwent plastic surgery on her fingers and toes about 20 years earlier and had artificial joint replacement of her left knee 2 years earlier. She had taken only prednisolone (PSL) 2.5 mg/day without DMARDs since about 1989, and disease activity had been almost stable during this time. She has concomitant chronic renal failure caused by IgA nephropathy and has been

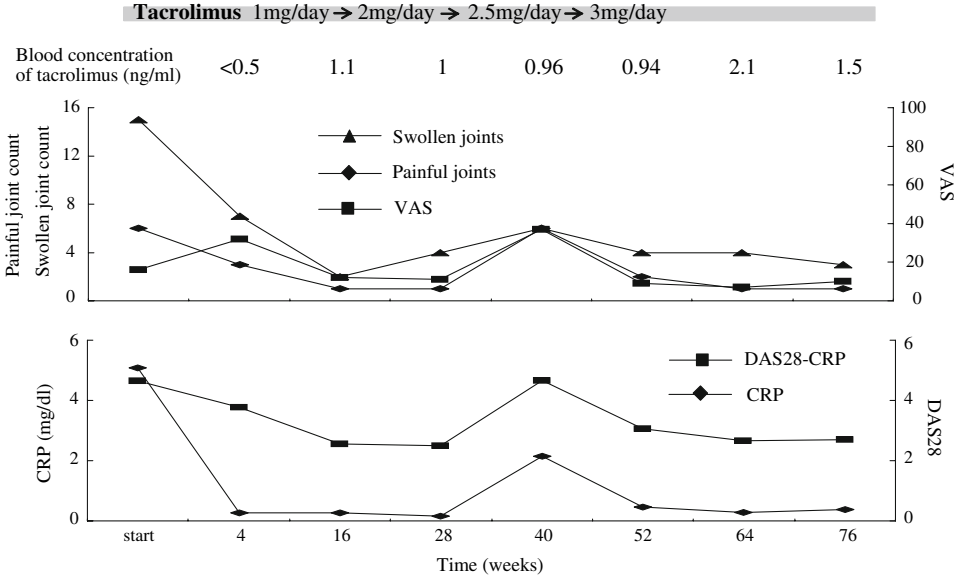


**Fig. 1** Clinical course of case 1 from the start of treatment with tacrolimus to date. Medication contents and blood concentration of tacrolimus are represented in the upper part. Change of swollen/painful joint counts and visual analog scale (VAS) are shown in the upper graph, C-reactive protein (CRP) level and disease activity score of 28 joints (DAS28) in the lower graph. In case 1, each value was improved 4 weeks later and a good clinical condition was maintained for a while. Although disease activity increased slightly for a short time (at 40–44 weeks), it improved again thereafter

**Table 2** Clinical course of case 1

| | | Start | 4 weeks | 28 weeks | 52 weeks | 76 weeks |
|---|---|---|---|---|---|---|
| DAS28[a] | Score | 4.65 | 3.77 | 2.50 | 3.06 | 2.70 |
| | Activity | Moderate | Moderate | Remission | Low | Low |
| | EULAR response | – | Moderate | Good | Good | Good |
| ACR improvement | | – | NA | 70 | 20 | 70 |

*EULAR* the European League Against Rheumatism, *ACR* the American College of Rheumatology, *NA* ACR 20 response was not achieved

[a] DAS28 is evaluated using the CRP level

receiving hemodialysis therapy from 2002. Recently her arthralgia worsened. In particular, she complained of strong pain in her left elbow joint and bone destruction was observed on plain X-ray films of the left elbow. Artificial joint replacement of the left elbow was not possible due to the vascular access in her left forearm for hemodialysis. Therefore, she was started on tacrolimus (1 mg/day) in November 2006. She had five painful joints and four swollen joints. VAS was 64 mm. CRP level was 0.266 mg/dl and ESR was 10 mm/h. DAS28 using the CRP level was 3.84, showing moderate activity. She also had concomitant renal anemia (hemoglobin 8.4 g/dl), thus we again used the CRP level when evaluating DAS28, as for Case 1. Rheumatoid factor was negative (Table 1). Liver function was normal (GOT 11 U/l, GPT 9 U/l, LDH 165 U/l, $\gamma$-GTP 11 U/l). At 24 weeks, joint swelling almost disappeared. CRP level has consistently stayed within the normal range from starting on tacrolimus to date (Fig. 2). At 52 weeks, DAS28 decreased to 2.90 and a moderate response was achieved (Table 3). However, painful joint count and VAS have not greatly changed (Fig. 2). Clinical improvement seems difficult to achieve because joint destruction has already progressed during the long disease duration. Tacrolimus dose was gradually increased to 3 mg/day without any side effects, and its blood concentration was within the margin of safety (0.64–5.0 ng/ml) (Fig. 2).

**Table 3** Clinical course of case 2

| | | Start | 4 weeks | 28 weeks | 52 weeks |
|---|---|---|---|---|---|
| DAS28[a] | Score | 3.84 | 3.48 | 3.24 | 2.90 |
| | Activity | Moderate | Moderate | Moderate | Low |
| | EULAR response | – | No | No | Moderate |
| ACR improvement | | – | NA | NA | NA |

[a] DAS28 is evaluated using the CRP level

## Discussion

In the ACR guidelines, appropriate DMARDs (in particular MTX) are recommended for initial RA treatment. However, the management of patients with RA and renal failure

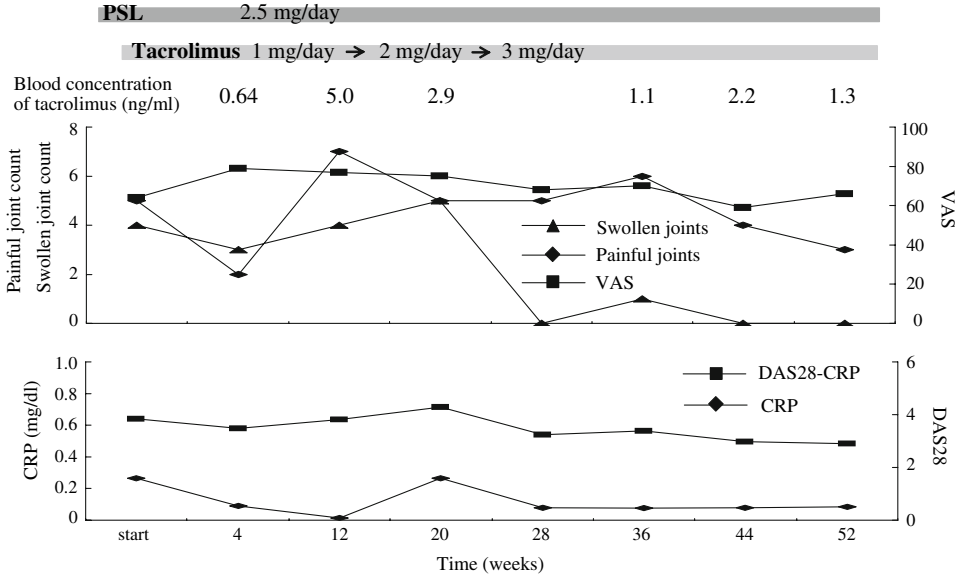


**Fig. 2** Clinical course of case 2 from the start of treatment with tacrolimus to date. Each item is shown the same as Fig. 1. In case 2, swollen joint count and DAS28 were improved 28 weeks later. From 44 weeks, DAS28 has decreased to <3.20 and has shown low activity

represents a therapeutic dilemma, as most DMARDs have a certain degree of nephrotoxicity. Special attention must be paid to a possible increase in toxicity and dose adjustment of the drugs. Our two patients are long-term sufferers of RA and their joint destruction has already progressed to Stage IV. They could not receive most of the DMARDs including MTX after their renal function worsened. In Japan, leflunomide, infliximab, etanercept, and tacrolimus have been approved as new drugs for RA after MTX and RA treatment has progressed greatly. However, clinical information about the safety of these new drugs for RA patients with renal impairment has not yet been available enough.

Oral tacrolimus 1.5–3 mg/day was approved for the treatment of other DMARDs-resistant RA in 2005. Tacrolimus is a macrolide lactone with potent immunosuppressive properties. It is used to prevent rejection of organ transplants and its pharmacokinetics has been described in several studies. After oral dosing, it is metabolized by the cytochrome P450-3A4 isoform that is present in the liver and in the mucosa of upper gastrointestinal tract. Most of the administered dose is recovered in feces, and less than 2% is excreted in urine as unchanged form. Since bile is the principal route of elimination, no changes in the dosing regimen of tacrolimus are necessary in patients with renal impairment or patients undergoing hemodialysis [6–9]. The mechanism of tacrolimus in T cells is known to diminish dephosphorylation of calcineurin leading to the synthesis of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), and interferon-γ (IFN-γ). Furthermore, tacrolimus is thought to regulate osteoclast differentiation by affecting not only T cells indirectly but also osteoclasts directly [5]. Tacrolimus therefore has the potential of improving joint inflammation and retarding bone destruction. Some clinical studies, such as a Phase II 6-month double-blind trial of RA patients who had failed MTX therapy [10] and a 12-month open-label study of tacrolimus as monotherapy in RA patients [11], demonstrated the safety and efficacy of tacrolimus for RA treatment.

There are the following reports about the use of MTX for patients with renal dysfunction. MTX is not recommended in patients with creatinine clearance <10 ml/min because MTX is primarily cleared by the kidney and up to 90% of the dose is excreted in urine as an unchanged form [1]. Bressolle et al. suggested that individual testing is required rather than a general decrease of the MTX dose based only on creatinine clearance [12]. Regarding dialysis, hemodialysis clearance of MTX using high-flux membranes has been previously reported to be 92.1± 10.3 ml/min [13], although peritoneal dialysis, conventional hemodialysis, hemoperfusion, and plasmapheresis are reported to be ineffective for MTX intoxication [1]. Besides, there have been several cases of life-threatening pancytopenia caused by low-dose MTX therapy in RA patients undergoing hemodialysis. Based on these reports, Basile et al. emphasized that MTX must not be prescribed for dialysis patients, at least for the treatment of RA [1].

On the other hand, leflunomide which was approved as one of the DMARDs in 2003 may be used in patients on hemodialysis without a reduction of the dose [2, 3]. However, cases of the death by interstitial pneumonia were reported in succession in the several years after leflunomide became available in Japan, and therefore its use tends to be limited.

Infliximab and etanercept, which are biological agents targeting the inflammatory cytokines were approved in 2003 and in 2005, respectively. Infliximab is a chimeric

anti-TNF-α monoclonal antibody and needs to be administered in combination with MTX. There were a few reports abroad showing that infliximab was effective and safe as monotherapy in RA patients on hemodialysis [14, 15]. In principle, monotherapy of infliximab is not approved in Japan. Etanercept, on the other hand, is a soluble TNF-α receptor fusion protein and may be administered without MTX. According to a clinical study of its pharmacokinetics in patients with chronic renal failure on hemodialysis, it is feasible to administer etanercept to such patients without adjusting the dose [4].

Considering the above-mentioned pharmacokinetics and effect on joint destruction, etanercept or tacrolimus is thought to be appropriate for our two patients' treatment. However, etanercept carries a higher risk of infection as a side effect and its medical costs are higher compared with tacrolimus. Besides, tacrolimus has better compliance due to its oral administration. For these reasons, we chose tacrolimus for their treatment. To our knowledge, these are the first case reports regarding the usefulness of tacrolimus for RA patients on hemodialysis. We started its administration at 1 mg/day while being careful of side effects by monitoring its trough blood concentration. Both patients take 3 mg/day tacrolimus at present without the need for withdrawing treatment due to adverse events or lack of efficacy.

In conclusion, we described two cases in which tacrolimus was beneficial for improving clinical outcomes, suggesting that it can be a good option for the treatment of RA patients undergoing hemodialysis. Needless to say, we must not forget the monitoring of blood concentration of tacrolimus for prevention of side effects. Since our suggestion is based on only two clinical observations, further experience is necessary to support its use in such patients.

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