Mod Rheumatol (2008) 18:293–295
DOI 10.1007/s10165-008-0041-4

CASE REPORT

Use of etanercept in a patient with rheumatoid arthritis on hemodialysis

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Received: 5 November 2007 / Accepted: 6 December 2007 / Published online: 27 February 2008

Abstract Disease-modifying anti-rheumatic drugs (DMARDs) are typically used for the therapy of rheumatoid arthritis (RA), but most have some nephrotoxicity. In several clinical studies, etanercept had fewer adverse effects on renal function than other DMARDs. We report the case of a 64-year-old woman with RA and renal insufficiency on hemodialysis treated using etanercept therapy. This case suggests that etanercept therapy might be effective in the short term for such patients.

Keywords Etanercept · Hemodialysis · Rheumatoid arthritis

Introduction

Therapy for rheumatoid arthritis (RA) is typically characterized by sequential use of disease-modifying anti-rheumatic drugs (DMARDs). Most DMARDs have some nephrotoxicity. Because some are excreted renally and their clearance is influenced by renal function, the blood concentration of these drugs may increase in patients with renal insufficiency. Thus, special attention is required to counteract the possible increase in toxicity and to adjust the dose of the drugs used to treat in these patients. Several clinical studies have reported that tumor necrosis factor α inhibitors (anti-TNFα, e.g., etanercept) have fewer adverse effects on renal function, so these agents are considered as alternative therapies. Etanercept is a human fusion protein that combines two extracellular binding domains of the p75 form of the TNF receptor with the Fc portion of a human IgG1 antibody molecule. This drug inhibits activity of TNF-α/lymphocytotoxin-α (TNFα/LTα), competitively binding to the pro-inflammatory cytokine and preventing interactions with cell-surface receptors. Etanercept has been shown to be extremely effective for RA and psoriasis [1]. However, little is known regarding the use of etanercept in patients with RA and renal insufficiency on hemodialysis (HD). We describe herein the case of a woman with RA on HD who was successfully treated using etanercept in short-term follow up.

Case report

A 64-year-old Japanese woman was referred to our hospital due to joint tenderness and swelling in the wrists, shoulders and knees. RA had been diagnosed at 63 years old. Past history showed end-stage renal disease secondary to chronic glomerulonephritis leading to HD at 62 years old. Although she was receiving steroid therapy (prednisolone 10 mg/day), her condition had not improved. Laboratory evaluation revealed: white blood cell count, 10,460 per dl; C reactive protein (CRP), 5.0 mg/dl; positive result for rheumatoid factor (119 IU/ml); negative results for anti-nuclear antibodies; and disease activity score 28-CRP4 (DAS28-CRP4), 5.98. As steroid therapy was proving ineffective, administration of etanercept, at a dose of

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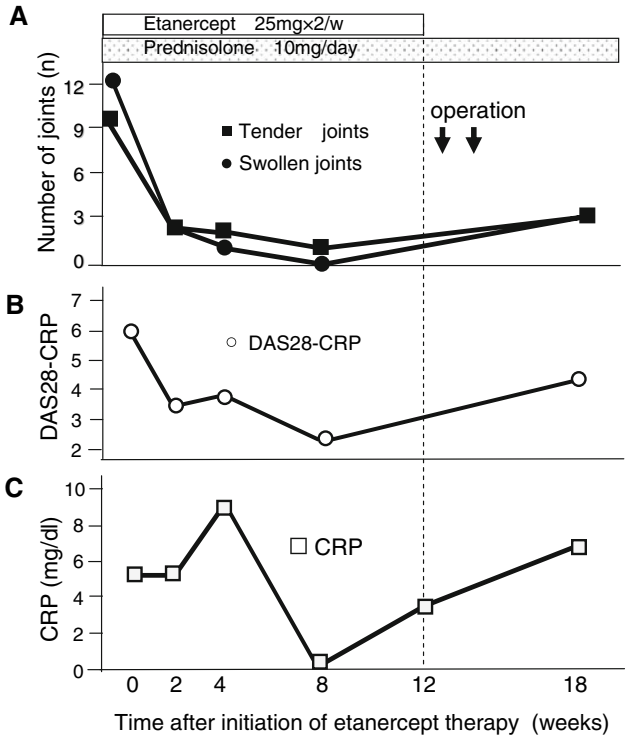

Fig. 1 Clinical course of the patient. She received subcutaneous injections of etanercept (25 mg) twice a week. Prednisolone (10 mg/day) was given concomitantly. **a** Counts of swollen (*filled circles*) and tender joints (*filled squares*), **b** disease activity score (*DAS*) 28-CRP4 (*open circles*), **c** CRP (*open squares*) were evaluated every two weeks. *Operation* means surgery for cataracts of both eyes

50 mg/week, was started for relief of symptoms. After two weeks, arthritis improved markedly with dramatic reductions in the number of tender and swollen joints (Fig. 1a). After eight weeks of treatment, CRP decreased to 0.4 mg/dl and DAS28-CRP4 decreased from 5.98 to 2.55 (Fig. 1b). On the basis of European League Against Rheumatism (EULAR) criteria this patient was classified as good responder. The patient continued to receive etanercept injections twice a week and clinical effects were maintained. However, after 12 weeks of therapy, she discontinued injections prior to undergoing cataract surgery. Clinical effects were maintained for at least 18 weeks without significant adverse events.

Discussion

Etanercept has been reported as a safe and effective medication for RA, with fewer effects on renal function than other DMARDs. Since etanercept is a fusion glycoprotein, consisting entirely of human protein components, it is expected to undergo proteolysis. Metabolism occurs through peptide and amino acid pathways with either recycling of amino acids or elimination in bile and urine [2]. No unchanged drug is found in the urine. However, the details of this metabolism are not well understood. Don et al. [3] demonstrated the safety of etanercept in six non-RA patients with chronic renal insufficiency on HD. The pharmacokinetics of etanercept in HD patients resembled those in patients with normal renal function. Comparison of pre- and post-dialysis concentrations indicated that HD does not appear to affect etanercept clearance, and that etanercept clearance is unaffected by renal function. However, little is known regarding the use of etanercept in patients with RA complicated by renal insufficiency and requiring HD. In the present case, etanercept was used due to the severity of symptoms. This treatment led to resolution of clinical symptom without any significant adverse effects or events during injection. This suggests that etanercept can be used, at least in the short-term, for patients with RA, even with renal insufficiency on HD. But, renal insufficiency is characterized by impaired host defenses, which are compromised further by HD. Reduced renal clearance of unknown toxins and administration of immunosuppressive medications lead to aberrant immune regulation and may cause serious and sometimes fatal infections. Thus, special attention is required when administering etanercept to these patients.

This report shows an alternative choice of treatment for RA patients with renal insufficiency on HD. DMARDs typically have some nephrotoxicity, and might aggravate the condition of such patients if not used with caution. Methotrexate (MTX), the most commonly used DMARD in RA, is excreted renally and is poorly cleared during HD. Severe pancytopenia has been reported during use of MTX for patients on HD, even at very low doses [4]. This suggests that considerable caution is needed when using this drug for patients on HD.

Salazosulfapyridine is also excreted renally, indicating that drug clearance is influenced by renal function. However, dialysis appears to affect clearance in HD, and the drug may be used if the dose is adequately reduced [5]. Bucillamine, D-penicillamine, actarit, and mizoribine are also excreted renally and the kidneys of patients on HD cannot excrete them naturally. But these drugs can easily be eliminated by HD when they are used in smaller doses, and there have been reports that RA patients on HD were responsive to them in small doses [6–9] Leflunomide is excreted in bile, and clearance is not influenced by renal function. Dose reductions do not appear to be required for patients on HD [10]. Tacrolimus is also excreted in bile, and clearance is not influenced by renal function [11], but some reports have described some nephrotoxicity for tacrolimus [12]. Some caution may be needed when using the drug for patients with renal insufficiency not undergoing HD. Anti-TNFα agents (etanercept, infliximab, and

adalimumab) are hydrolyzed at lysosomes and may not influence renal function. Previous case reports have demonstrated that response to treatment with infliximab without MTX is very good and that patients with RA on HD can tolerate this drug [13, 14]. We could not find any other reports describing use of etanercept in such patients. The present case study suggests that etanercept therapy might be effective in the short-term for RA patients with renal insufficiency on HD. Additional case studies are needed to establish the appropriate use of etanercept for RA patients on HD.

Conclusion

We report a case in which etanercept therapy was used successfully for a patient with RA on HD. Administration of etanercept may thus be useful for RA patients on HD in short term as an alternative treatment.

Acknowledgments The authors have no financial and personal relationship with the organization whose product or competing product plays a prominent role in this manuscript.

References

1. Stokes DG, Kremer JM. Potential of tumor necrosis factor neutralization strategies in rheumatologic disorders other than rheumatoid arthritis. Semin Arthritis Rheum. 2003;33:1–18.
2. Lee H, Kimko HC, Rogge M, Wang D, Nestorov I, Peck CC. Population pharmacokinetic and pharmacodynamic modeling of etanercept using logistic regression analysis. Clin Pharmacol Ther. 2003;73:348–65.
3. Don BR, Spin G, Nestorov I, Hutmacher M, Rose A, Kaysen GA. The pharmacokinetics of etanercept in patients with end-stage renal disease on haemodialysis. J Pharm Pharmacol. 2005; 57:1407–13.
4. Nakamura M, Sakemi T, Nagasawa K. Severe pancytopenia caused by a single administration of low dose methotrexate in a patient undergoing hemodialysis. J Rheumatol. 1999;26:1424–5.
5. Akiyama Y, Fujimaki T, Sakurai Y. Pharmacokinetics of salazosulfapyridine in a hemodialysis patient (in Japanese). Ryumachi. 2003;43:569–76.
6. Hamada K. The safety of actarit (mover) in hemodialysis patients with rheumatoid arthritis (in Japanese). Prog Med. 1997;17: 1652–7.
7. Kaizu K, Komine N, Uriu K, Ikeda M, Hashimoto O, Eto S. Bucillamine may be an effective anti-rheumatic drug in patients with end-stage renal disease—a case report (in Japanese). J Jpn Soc Dial Ther. 1994;27:1505–10.
8. Matthey F, Perrett D, Greenwood RN, Baker LRI. The use of D-penicillamine in patients with rheumatoid arthritis undergoing hemodialysis. Clin Nephrol. 1986;25:268–71.
9. Saisho K, Kurosawa O, Fukanoki T, Hanafusa A, Tajima N. Long-term use of mizoribine in rheumatoid arthritis patients on hemodialysis. Mod Rheumatol. 2001;11:132–5.
10. Beaman JM, Hackett LP, Luxton G, Illett KF. Effect of hemodialysis on leflunomide plasma concentrations. Ann Pharmacother. 2002;36:75–7.
11. Gruber SA, Hewitt JM, Sorenson AL. Pharmacokinetics of FK506 after intravenous and oral administration in patients awaiting renal transplantation. J Clin Pharmacol. 1994;34:859–64.
12. Andoh TF, Burdmann EA, Lindsley J, Houghton DC, Bennett WM. Enhancement of FK506 nephrotoxicity by sodium depletion in an experimental rat model. Transplantation. 1994;57:483–9.
13. Singh R, Cuchacovich R, Huang W, Espinoza LR. Infliximab treatment in a patient with rheumatoid arthritis on hemodialysis. J Rheumatol. 2002;29:636–7.
14. Hammoudeh M. Infliximab treatment in a patient with rheumatoid arthritis on haemodialysis. Rheumatology (Oxford). 2006; 45:357–9.