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The pharmacokinetics of etanercept in patients with end-stage renal disease on haemodialysis

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Abstract

Inflammation is strongly associated with malnutrition and cardiovascular risk in patients with chronic renal failure on haemodialysis (HD). The acute-phase inflammatory response, defined by the increased synthesis of positive acute-phase proteins, is stimulated by the production of such cytokines as interleukin 6 (IL-6), interleukin 1 (IL-1) and tumour necrosis factor-α TNF-α The availability of cytokine antagonists allows testing of the hypothesis that suppression of inflammation reverses the malnutrition–inflammation syndrome in HD patients. Etanercept is a soluble TNF-α receptor fusion protein used to suppress inflammation in rheumatoid and psoriatic arthritis. Its metabolism in HD patients is unknown. In a study designed to test the safety and pharmacokinetics of etanercept in HD patients, etanercept was administered to six HD patients with albumin levels above 4.2 g dL^{-1} and C-reactive protein levels <5 mg L^{-1} (five men, one woman, age range 34–59 years). Etanercept (25 mg) was administered subcutaneously twice weekly immediately after dialysis for 13–16 weeks. Etanercept concentrations were measured pre- and post-dialysis by ELISA. Concentrations were compared graphically to assess whether, firstly, dialysis affects etanercept apparent clearance and, secondly, etanercept kinetics were similar between HD patients and the more extensively studied psoriasis population with normal renal function (PS). The second stage examined model-based parameter predictions of the terminal elimination rate constant (k) for HD patients. Steady-state etanercept levels were comparable between HD and PS patients. Treatment with HD had no effect on etanercept levels. When etanercept was discontinued, the terminal rate constant for HD patients was not significantly different from that observed in PS patients. No adverse effects were noted during the 3-month treatment phase and subsequent 6-month follow-up. Albumin and C-reactive protein levels did not change in these non-inflamed patients during the study period. The pharmacokinetics of etanercept in patients with chronic renal failure on HD are similar to patients with normal renal function. It is, therefore, feasible to administer etanercept to HD patients without adjusting the dose

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Introduction

Etanercept is a fully human dimeric fusion protein containing the two extracellular ligand-binding domains of tumour necrosis factor-α (TNF-α) receptor (75 kDa) linked to the Fc portion of human immunoglobulin G1 (Goffe & Cather 2003; Olsen & Stein 2004). Etanercept thereby inhibits the activity of TNF-α, competitively binding to this pro-inflammatory cytokine and preventing its interaction with cell surface receptors. The dimeric structure of etanercept allows it to simultaneously bind two free, or receptor-bound, molecules of TNF-α at an affinity of 50–1000 times that of soluble monomeric forms of the TNF-α receptor (Stokes & Kremer 2003). TNF-α plays a critical role in the activation of innate and acquired immune responses. Unfortunately, persistence of the immune response can result in tissue injury rather than host defence (Ridker et al 1998b). Persistence can be overcome by TNF-α neutralizing strategies, which have been shown to be effective in a number of rheumatological disorders. Etanercept is currently approved for use in the treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis and juvenile rheumatoid arthritis (Stokes & Kremer 2003).

The acute-phase inflammatory response is a complex cascade of physiological, immunological and metabolic factors that regulates the release of interleukin (IL)-1, IL-2, IL-8 and TNF-α, increase in synthesis of a group of proteins, including C-reactive protein (CRP), and suppression of synthesis of negative acute-phase proteins, including albumin (Bistrain 1998). Although serum albumin concentration traditionally has been considered a marker of nutritional status and is a strong predictor of mortality in patients with end-stage renal disease (Lowrie & Lew 1990; Hakim & Levin 1993), recent studies suggest that the importance of inflammation in causing hypoalbuminaemia may rival that of protein intake (Kaysen et al 1995; Moshage 1997; Don & Kaysen 2000). The acute-phase response, as assessed by measurement of CRP or IL-6, is associated with increased risk of cardiovascular disease in the general population (Ridker et al 1998a, b). CRP and IL-6 levels are also higher in dialysis patients than in the general population (Pereira et al 1994), and markedly elevated CRP levels in dialysis patients are associated with hypoalbuminaemia and subsequent all-cause and cardiovascular mortality (Bologna et al 1998; Yeun & Kaysen 1998). Moreover, inflammation appears to be a more powerful predictor of mortality in haemodialysis (HD) patients than serum albumin concentration (Kaysen et al 1995; Don & Kaysen 2000).

The cause of inflammation in dialysis patients is multifactoral. In some patients with end-stage renal disease whose serologic markers of inflammation are augmented, clinical infections may contribute to the inflammatory response. However, in the majority of dialysis patients with elevated markers of inflammation, oxidative stress, exposure to dialysis membranes and other non-infectious entities appear to contribute to inflammation (Bistrain 1998; Don & Kaysen 2000). All-cause and cardiovascular mortality is also increased in dialysis patients with an activated acute-phase response, among whom a link between systemic inflammation and accelerated atherosclerosis has been suggested (Stenvinkel et al 1999). Although inflammation is associated with increased cardiovascular mortality, with the exception of HMG Co A reductase inhibitors, specific treatments directed at the inflammatory response are lacking. A number of therapeutic strategies are being developed to attenuate the inflammatory cascade and its untoward effect on patient survival, including potential treatment with etanercept. Since the metabolism of this large protein in patients with renal failure is unknown, the pharmacokinetics and safety of etanercept in this patient population must be determined before embarking on a study of efficacy.

Methods

Subjects

The protocol was approved by the Human Subjects Review Committee of the University of California Davis Medical Center and Dialysis Clinics, Incorporated. Informed consent was obtained from each patient. The criteria for enrollment included the absence of active infection or malignancy for the five years leading up to the study, except for basal or squamous cell carcinoma of the skin. Patients with HIV infection, a transcutaneous vascular access, patients taking corticosteroids in the last 90 days, abnormal liver tests, abnormal white blood cell count, or evidence of alcohol or drug abuse were excluded from participating in the study. A negative pregnancy test or being post-menopausal for greater than five years was required for women patients to enroll in the study. Six patients with end-stage renal disease who had been on HD for at least three months participated in this study. Five of the six patients had no significant residual renal function and patient 2 had a residual urea clearance of 8.9 mL min^{-1}. The demographics for the group are noted in Table 1.

Experimental design

A physical examination was performed and a complete blood count was obtained in all patients before participating in the study. Etanercept (25 mg) was administered by subcutaneous injection twice weekly at the end of the first and third dialysis treatment session of the week for a total of 13–16 weeks. Blood samples were drawn just before the administration of each dose during the first 3 weeks, and then weekly for the next 3 weeks. Following that, blood samples were obtained bi-weekly. During the second week of the study, blood samples were also obtained before, and following, the mid-week dialysis session, during which no etanercept was administered. The dialysis membranes used during the dialysis sessions were high-flux polysulfone membranes. The physical examination was repeated during the eighth week and at the end of the study.

Serum concentrations of etanercept were measured by a validated enzyme-linked immunosorbent assay (ELISA) method. This ELISA method utilized a sandwich format to measure etanercept. A mouse anti-TNFR monoclonal antibody was bound to the ELISA plate and used to capture etanercept in the standard, control or unknown samples. A polyclonal goat anti-TNFR:Fc antibody was added to complete the sandwich. A horseradish peroxidase-conjugated donkey anti-goat antibody was then used to detect the bound goat antibody. TMB-H_2O_2 substrate for horseradish peroxidase was added to generate a colorimetric reaction to quantify etanercept. The lower limit of quantification was 0.625 ng mL^{-1}; the accuracy of the ELISA was −13.6% to 13.6% and the precision was 0.65% to 14%.

Table 1 Demographics of study patients

Patient	Age	Gender	Ethnicity	Body mass index (kg m^{-2})
1	36	Male	Asian American	26.9
2	51	Male	African American	22.5
3	48	Male	African American	34.5
4	46	Female	African American	31.1
5	58	Male	African American	40.7
6	51	Male	Hispanic American	40.7

Assays were performed to measure serum levels of albumin, prealbumin, CRP, soluble interstitial cell adhesion molecule (sICAM), vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6). Serum albumin was measured using brome cresol green, prealbumin and CRP by rate nephelometry, and sICAM, VEGF and IL-6 by ELISA (HEMAGEN). All nephelometric and ELISA measurements were made in duplicate and the average of the values was used for calculations. The intra-assay CV for CRP was 0.35% and inter-assay CV 5.5%. The intra-assay CV for IL-6 was 0.32% and inter-assay CV 8.7%. The intra-assay CV for VEGF was 5.4% and inter-assay CV 7.3%. The intra-assay CV for sICAM was 1.7% and inter-assay CV 15.9%.

Pharmacokinetic analysis

The etanercept pharmacokinetics in HD patients were evaluated in three stages. In the first stage, two comparisons were made to assess whether dialysis affects etanercept apparent clearance and whether renal failure alters etanercept kinetic profiles from that of the more extensively studied psoriasis (PS) population with normal renal function. The second stage examined the PS population PK model's capability of predicting the etanercept distribution and clearance in patients with end-stage renal disease. To accomplish this, we examined the disappearance of etanercept following discontinuation (terminal phase concentrations). These were fit for each HD patient using the PS population model, yielding model-based parameter predictions of the terminal elimination rate constant (k_e) for the HD patients. Non-compartmental estimates were also computed and compared with those predicted by the PS population model. For the non-compartmental analysis, individual regressions were performed on the $\log_e$-transformed data to yield elimination rate constant (k_e) estimates. Maximization of the adjusted R^2 statistic was used to determine the data points supporting each regression. The population model predictions of k_e (time-weighted) and the non-compartmental estimates were compared graphically to further assess similarity and model suitability.

Finally, the PS population model was used to predict the apparent clearances (CL/F) for the HD patients. These CL/F predictions were compared with the CL/F distribution expected from an identical sample size ($n = 6$) to further evaluate the similarity of the two populations.

The population pharmacokinetic analysis was carried out using NONMEM, version V software (NONMEM Project Group, University of California, San Francisco, 1996). The non-compartmental (NC) parameters and statistical processing were derived using SAS version 6.2 (SAS Institute Inc., Cary, NC, USA, 1989).

Results

Pharmacokinetic analysis

The pre- and post-dialysis serum concentrations of etanercept were compared graphically. Figures 1 and 2 display the serum concentration of etanercept from week two of the study, pre-and post-dialysis. The box plot of Figure 1 demonstrates that the median serum concentrations for etanercept pre- and post-dialysis are similar, with no significant change in levels due to dialysis. Figure 2 displays the observed concentrations versus time after last dose for the dialysis-sampling window. Pre-dialysis sample times were in the range 43.83–45.23 h and the post-dialysis sample times were in the range 46.67–48.58 h after the last administration of drug. The concentrations are connected within an individual to highlight the inter- and intra-patient variances. Three of the patients show an increase in etanercept concentration with time. This increase could be the result of the long absorption phase of etanercept following subcutaneous administration as these sampling times are within the Tmax range. Based on data presented in Figures 1 and 2, there is no discernible clearance of etanercept due to HD.

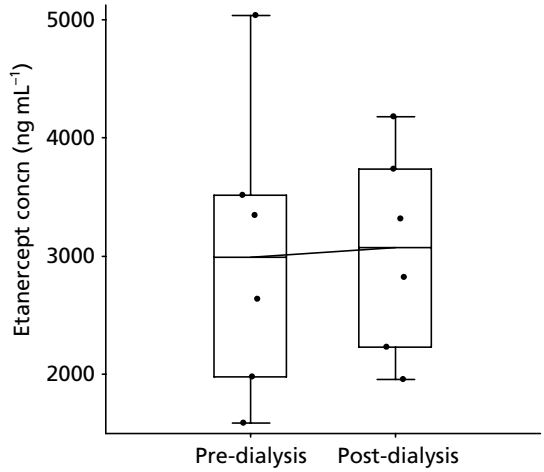

Figure 1 Serum concentrations of etanercept pre- and post-dialysis during week 2 of treatment in HD patients.

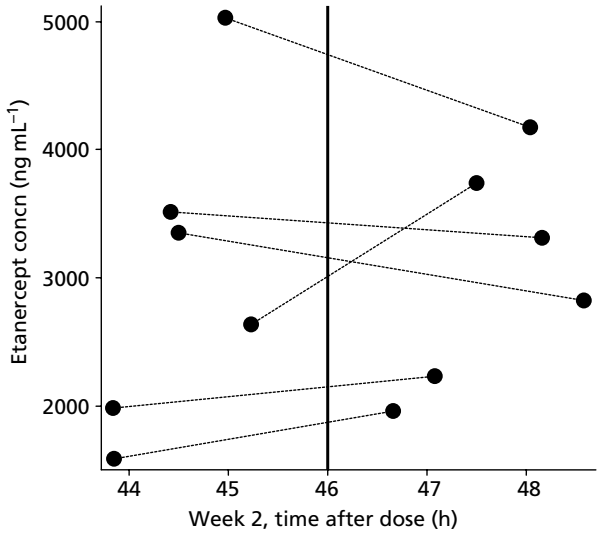

Figure 2 Concentration of etanercept versus time in HD patients after the last dose of drug for the dialysis sampling window. See Results section for details.

The differences in pre- and post-dialysis concentrations were used to assess the influence of dialysis on etanercept clearance (CL/F). The observed concentrations in HD patients were superimposed on the concentration distributions simulated from a population pharmacokinetic model developed in PS patients with normal renal function (Nestorov et al 2004). For comparative purposes, the model-simulated concentration distributions were represented by 2.5, 25, 50 (median), 75 and 97.5 percentiles. HD-data/PS model compatibility was not tested formally (e.g. posterior predictive check) because the small HD patient sample size ($n = 6$) would result in lack of power for such comparisons. Figure 3 displays the serum etanercept concentrations in the HD patient superimposed on the simulated etanercept concentration distribution of the PS population. The initial variation in the disposition parameters is reflected by the rapid rise in etanercept concentration during weeks 1 and 2, followed by the downward adjustment during weeks 3–5, which tapers to steady-state by week 12. The PS population pharmacokinetic model predicts a ~25% lower CL/F for the first two weeks followed by a 32% increase in CL/F relative to steady-state predictions. This variation, discussed in detail by Nestorov et al (2004), is brought about by either an immune response of the organism or a redistribution of the free soluble TNF-α after the first administrations of etanercept, or both of these factors.

Generally, the etanercept concentrations in the HD patients parallel the trajectory of the simulated concentrations of etanercept in PS patients with normal renal function and fall well within the 2.5 and 97.5 percentiles on Figure 3. The latter is evidence that both the apparent volumes of distribution and the apparent clearances of etanercept in the six HD subjects cannot be distinguished from those derived for psoriasis patients with normal renal function.

The individual concentration profiles were constructed from the population PK model predicted parameters and compared graphically with the observed data. Figure 4 displays the PS population pharmacokinetic model (posterior Bayes) predictions of the terminal phase concentrations for each patient. The non-compartmental predictions based on individual regression estimates are also displayed. The adjusted R^2 statistics were greater than 0.9 for every patient, except patient 3. Patient 3 had only three concentrations sampled after the last dose. Thus, it was difficult to establish that these concentrations were sampled in the terminal phase. The 92.5-h sample for patient 4 was omitted from the non-compartmental regression analysis because of its substantial inflation of residual error (and corresponding decrease in adjusted R^2). The population model predictions did not demonstrate an increased lack-of-fit relative to the non-compartmental predictions, and

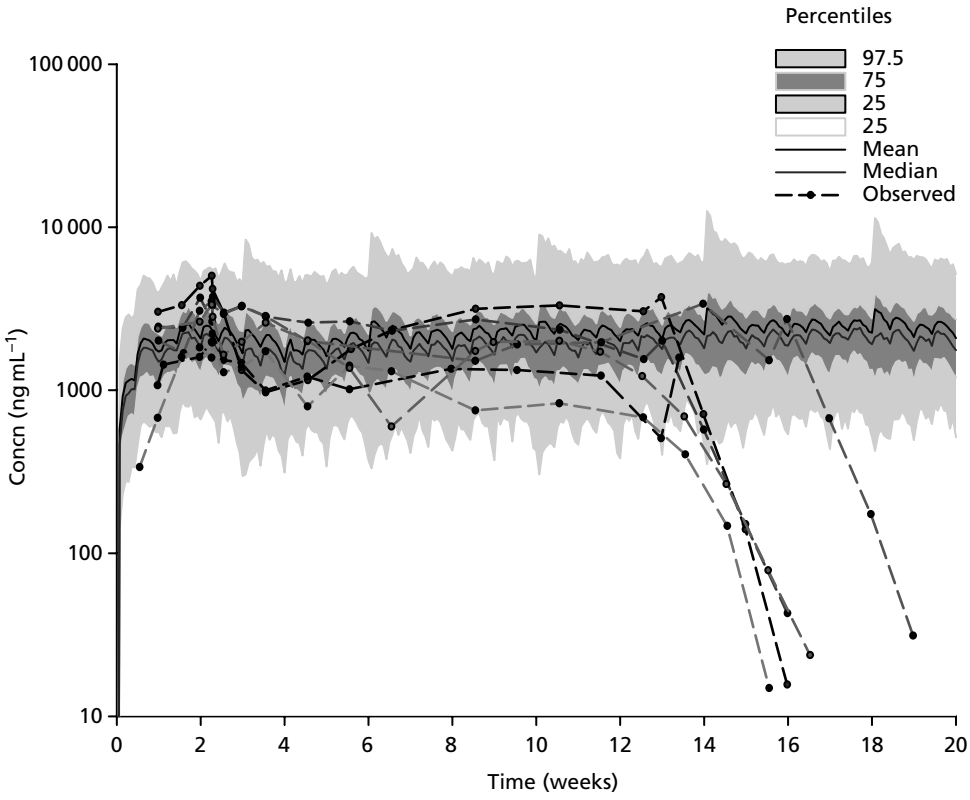

Figure 3 Serum concentrations of etanercept concentrations in the HD patients superimposed on the simulated etanercept concentration in the PS population. When etanercept was discontinued, the terminal rate constant was not significantly different to that observed in the PS population with normal renal function.

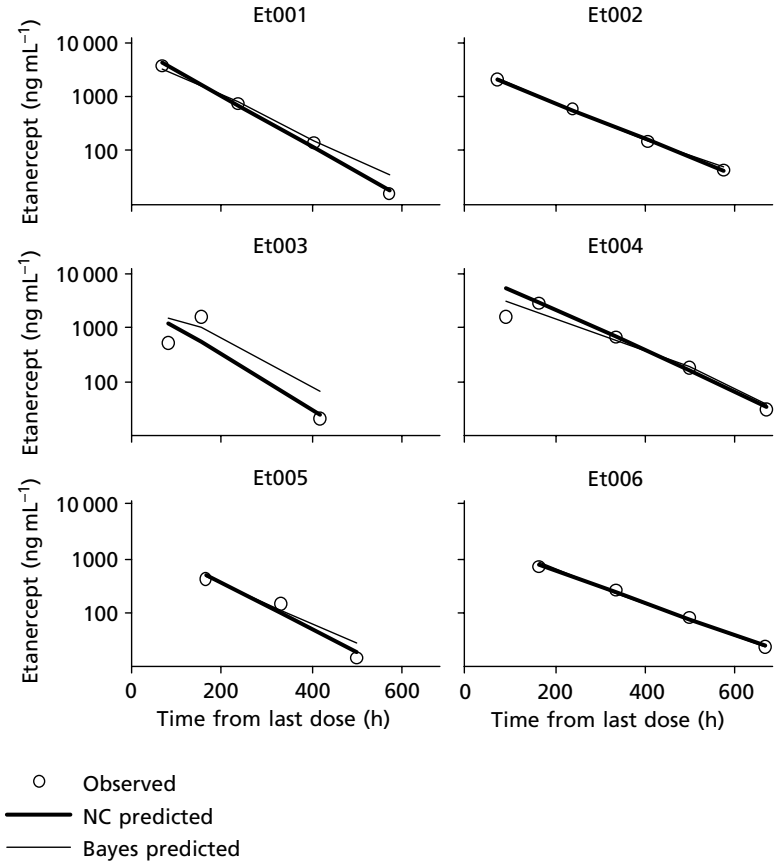

Figure 4 The PS population pharmacokinetic model (posterior Bayes) predictions of the terminal phase concentrations of etanercept for the 6 HD patients. Bayes and non-compartmental (NC) estimates of the individual patients' elimination rate constants (or slopes): patient 1, Bayes 0.0090176193, non-compartmental, 0.0107320372; patient 2, Bayes, 0.0079494884, non-compartmental, 0.0076989069; patient 3, Bayes, 0.0099637686, non-compartmental, 0.0114696393; patient 4, Bayes, 0.0079401578, non-compartmental, 0.0087822213; patient 5, Bayes, 0.0091306228, non-compartmental, 0.0098246372; patient 6, Bayes, 0.0077330222, non-compartmental, 0.0067456563.

both predictions track the terminal phase data for the HD patients. This supports the concept that the pharmacokinetics of etanercept in patients with normal renal function closely resembles that of patients with end-stage renal disease.

The PS population pharmacokinetic model also was used to predict the steady-state CL/F. These predictions were a function of each patient's weight and sex, and also the magnitude of inter-patient variability. To assess the similarity of CL/F between the HD and PS populations, the median and range of the CL/F predictions were compared with the expected median and range in a simulated population of six PS patients. The steady-state model predicted CL/F values for the six HD patients are displayed in Figure 5. To assess the similarity in CL/F with the PS population (in both central tendency and dispersion), the simulation previously described was performed. The expected median and range of the PS population CL/F are also displayed in Figure 5. The medians of the two populations are similar. Two CL/F predictions (patients 3 and 5) lie outside the predicted range of the PS patients. Due to the small sample size, it is difficult to conclude if the inter-patient variability is greater in HD patients compared with PS patients.

Acute-phase proteins

The serum concentration of serum albumin and other acute phase proteins at baseline and at the last administration day of etanercept (completion point) are shown in Table 2. The baseline levels of these proteins were within the normal range for healthy control subjects. Treatment with etanercept had no significant effect on serum albumin and other acute-phase proteins in these non-inflamed end-stage renal disease patients.

Adverse events

There were no serious clinical or laboratory adverse events during the study and for at least three months after the completion of the study.

Discussion

The safety of etanercept has been demonstrated in more than 130 000 patient-years of exposure in both controlled

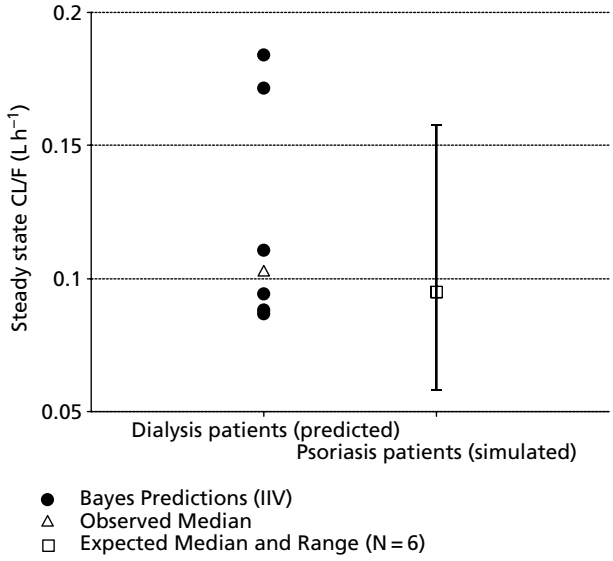

Figure 5 The CL/F of etanercept for the 6 HD patients based on Bayesian prediction and the mean ± s.d. simulated CL/F of etanercept for the PS population with normal renal function. The CL/F predictions by individual patient are: patient 1, 0.0868300108; patient 2, 0.094197336; patient 3, 0.1713848369; patient 4, 0.0882882922; patient 5, 0.1841287503; patient 6, 0.1106437652. Median, minimum and maximum CL/F values for the PS group were 0.0952184207, 0.058301161 and 0.1576559529, respectively.

Table 2 Serum acute-phase protein concentrations before (baseline) and on final etanercept administration day

Parameter	Baseline	s.e.	Etanercept	s.e.	t	*P*
Albumin	4.717	0.0628	4.649	0.110	0.831	0.444
sICAM	314.8	20.6	303.4	26.1	0.827	0.446
VEGF	386.8	81.7	372.9	84.9	0.601	0.574
CRP	0.245	0.057	0.342	0.022	−1.295	0.252
Pre albumin	41.4	3.41	46.5	3.55	−0.935	0.393

clinical trials and in post-marketing surveillance (Goffe & Cather 2003). Studies in normal control subjects after a single 25-mg subcutaneous injection of etanercept demonstrated that the drug is absorbed slowly. Concentrations of etanercept peak approximately 50 h after administration, and the drug has a half-life of 68 ± 19 h in healthy subjects and 102 ± 19 h in rheumatoid arthritis patients with normal renal function (etanercept package insert). The apparent clearance was $132 \pm 85\,\mathrm{mL\,h^{-1}}$ with an apparent volume of distribution of 12 ± 6 L (Korth-Bradley et al 2000). The metabolism of etanercept is not well understood, but it is assumed the etanercept–TNF complex is metabolized through peptide and amino acid pathways with either recycling of amino acids or elimination in bile and urine (Lee et al 2003).

Results of this study indicate that the pharmacokinetics of etanercept in patients with end-stage renal disease is similar to that in patients with normal renal function. Moreover, HD did not lower the serum levels of etanercept, and thus does not alter the clearance of the drug. This is to be expected since the molecular weight and size of etanercept is beyond the clearance range of current haemodialysers. The graphical comparison of the pre- and post-dialysis concentrations indicated that dialysis does not appear to affect etanercept clearance in HD patients. The PS population pharmacokinetic model was concluded to be adequate for prediction of the HD patient population. Overall, there was no marked difference in concentrations and PK parameter distributions between the HD and PS population. While the HD inter-patient variability in CL/F may be slightly greater than that of the PS patients (which is not unexpected), the increase does not appear to be clinically relevant, in as much as the median CL/F value observed in this study ($0.103\,\mathrm{L\,h^{-1}}$) is similar to the mean CL/F observed in healthy subjects ($0.132\,\mathrm{L\,h^{-1}}$).

Etancercept was well tolerated by patients with end-stage renal disease, as there were no significant adverse effects or events during the 13- to 16-week study period. In controlled trials, the most frequent adverse event in patients treated with etanercept was mild to moderate injection site reactions (erythema/pain/swelling), which occurred in approximately 37% of patients receiving the drug (Goffe & Cather 2003). In the initial studies, conducted in patients who received etanercept in long-term trials (up to five years), the rates of infection requiring hospitalization or intravenous antibiotics is comparable with rates seen in the placebo control group (Goffe & Cather 2003). However, with greater use of TNF-α antagonists, there have been more recent case reports and small series which suggest that etanercept increases mortality if given to patients with established sepsis. The risk of opportunistic infections, including tuberculosis and histoplasmosis, appears to be increased in patients receiving TNF-α antagonists (Olsen & Stein 2004). Use of TNF-α antagonists also has been associated with lymphoma, although a causal relationship has not been established (Brown et al 2002). Antibodies to double-stranded DNA have developed in 4% of patients with rheumatoid arthritis treated with etanercept, although etanercept-induced systemic lupus erythematosus is rare (Shakoor et al 2002). None of the patients in the current study developed anti-nuclear antibodies.

Etanercept had no effect on the plasma level of serum albumin, CRP and the other acute-phase proteins. This is not surprising given that the patients enrolled in this study were stable, infection-free HD patients with no evidence of underlying activation of the systemic inflammatory response. Since the baseline level of acute-phase proteins was within normal range, treatment with a TNF-α antagonist did not appear to affect these levels. In contrast, etanercept treatment decreased CRP levels in patients with active rheumatoid arthritis and psoriatic arthritis. Consequently, etanercept appears to decrease levels of inflammatory mediators only in patients with active inflammation.

Conclusions

The pharmacokinetics of etanercept in patients with chronic renal failure on haemodialysis are similar to those in patients with normal renal function. It is,

therefore, feasible to administer etanercept to HD patients without adjusting the dose.

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