CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

103950/0

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

Date: August 25, 2000 (final)

From: Lori A. Paserchia, MD

Through: Martin D. Green, PhD/Branch Chief, Pharmacology/Toxicology/DCTDA
Karen Weiss, MD/Director, DCTDA

Subject: Clinical Pharmacology Review of BLA 99-1490 (anakinra, Kineret™)

To: Center/Division/Office- DARP, OTRR
Clinical Reviewer- Jeff Siegel, MD

Please see attached review.

EXECUTIVE SUMMARY

IL-1 is a key mediator of immune and inflammatory responses. IL-1 may have a role in the joint injury associated with rheumatoid arthritis.

Endogenous interleukin-1 receptor antagonist (IL-1ra) is binds to the IL-1 receptor and blocks the action of IL-1. IL-1ra has a similar binding affinity to the IL-1 type-I receptor as IL-1 but is not capable of transducing the signal. IL-1 has such a high efficacy (i.e., response for a given percent receptor occupancy) that an excess of IL-1ra is needed to block the action of IL-1. Animal models *in vivo* have demonstrated that the use of anakinra reduced inflammation and joint swelling.

Anakinra (r-metHuL-1ra; Kineret™) is an N-terminal-methionylated, non-glycosylated version of IL-1ra from Amgen Inc. that is produced using an E coli expression system. The proposed indication is "for use in patients 18 years or older for the reduction in signs and symptoms of moderate to severe active rheumatoid arthritis (RA) who have had an inadequate response to one of more disease-modifying antirheumatic drugs (DMARDs). Anakinra can be used in combination with [redacted]. The proposed dosing regimen is [redacted] subcutaneous (SQ) daily when using [redacted] the pre-filled syringes:

[redacted]

The sponsor submitted 12 studies and 1 report ito support the pharmacokinetic (PK) section of the labeling. Ten of these 12 studies are PK studies. A PK study is one where a PK analysis was performed and PK parameters were derived. A non-PK study is one where plasma levels of anakinra were collected but PK parameters were not derived.

Based on the PK results submitted in this BLA, anakinra demonstrates dose proportional increases in exposure (area under the curve and maximum plasma concentration) during single- and multiple dosing in the 0.5 to 4.0 mg/kg dose range in subjects with RA. Minimal accumulation of anakinra is seen during 24 weeks of daily SQ bolus dosing with a dosing range of 30-150 mg as a fixed-dose.

The PK profile of anakinra, when given SQ, is absorption-rate-limited in the dose range studied in this BLA (i.e., flip-flop kinetics). The apparent clearance of anakinra increases with increasing creatinine clearance and body weight. Gender and age are not significant factors for the apparent clearance, after adjustment for creatinine clearance and body weight. The pharmacokinetic profile of a single dose of 1.0 mg/kg administered iv is significantly altered in subjects with chronic renal failure. Plasma clearance of IL-1ra is decreased, and exposure to IL-1ra is greater, in subjects with chronic renal failure compared to that in healthy subjects. The safety and PK profiles of IL-1ra, when administered as a daily SQ bolus to subjects with chronic renal failure, are unknown and should be studied during Phase 4 in order to permit effective labeling for this patient population.

A formal study to determine the potential for drug-drug interactions between methotrexate (or any other type of disease modifying anti-rheumatic drugs) and anakinra has not been conducted.

Clinical Pharmacology Review

Pharmacokinetic Studies (Reviewed):

Studies with bolus SQ injection in subjects with RA (to-be-marketed route of administration)

Population PK study

Studies with continuous SQ injection in subjects with RA

Bioavailability and Formulation Comparison study

Studies with intravenous injection in various subject populations

Non-Pharmacokinetic Studies:

Studies with bolus SQ injection in subjects with RA (to-be-marketed route of administration)

Studies with continuous SQ injection in subjects with RA

Pharmacokinetic Studies (Not Reviewed):

Studies with intravenous injection in healthy subjects

Individual Study Review:

The Product

IL-1 is a key mediator of immune and inflammatory responses. Not typically found in plasma and other body fluids under normal conditions, IL-1 production is induced in response to inflammation, immunologic reactions and tissue injury. It is this induction and response that may have a role in the joint injury associated with rheumatoid arthritis.

Endogenous interleukin-1 receptor antagonist (IL-1ra) is a 17.1 kD (152 amino acids) protein that binds to the IL-1 receptor and blocks the action of IL-1. Anakinra (r-metHuL-1ra; Kineret™) is an N-terminal-methionylated, non-glycosylated version of IL-1ra with 153 amino acids and a molecular weight of 17.3 kD that is produced using an E coli expression system. The final product is comprised of anakinra, sodium citrate, sodium chloride, EDTA and polysorbate-80; it is preservative-free.

IL-1ra has a similar binding affinity to the IL-1 type-I receptor as IL-1 but is not capable of transducing the signal. IL-1 has such a high efficacy (i.e., response for a given percent receptor occupancy) that an excess of IL-1ra is needed to block the action of IL-1. Animal models *in vivo* have demonstrated that the use of anakinra reduced inflammation and joint swelling.

The **proposed indication** is "for use in patients 18 years or older for the reduction in signs and symptoms of moderate to severe active rheumatoid arthritis (RA) who have had an inadequate response to one of more disease-modifying antirheumatic drugs (DMARDs). Anakinra can be used in combination with

The **proposed dosing regimen** is 1 mg/kg subcutaneous (SQ) daily when using

ne pre-filled syringes:

Introduction to the Review

The sponsor submitted 12 studies and 1 report in support of the PK section of the labeling. Ten of the 12 studies were pharmacokinetic (PK) studies: Protocols 0501, 0502, 100788, 970189, 0530, 0555, 0563, 0503, 0540 and 0541. A PK study is one where a PK analysis was performed and PK parameters were derived. A non-PK study is one where plasma levels of anakinra were collected but PK parameters were not derived.

Protocols 0501 and 0502 investigated the proposed route of administration (bolus SQ injection) in the intended population, patients with RA. Alternatively, anakinra was administered as a continuous SQ injection in Protocol 970189. Protocol 100788 was a population PK study. Protocol 0530 was a bioavailability and formulation comparison study where an older formulation was administered iv and SQ, and its PK profiles were compared to the SQ PK profile of a new formulation (that became the to-be-marketed [TBM] formulation).

While anakinra was administered intravenously (not SQ) in Protocol 0555, the results are useful since the study population was comprised of subjects with chronic renal failure (CRF) necessitating dialysis. For a similar reason, Protocol 0563 was reviewed because the study population was comprised of subjects with mild-moderate hepatic dysfunction. Amgen also conducted a comparison of the PK profiles in the subjects with CRF and subjects with hepatic dysfunction to the PK profile in healthy subjects (listed as number 8, "Report", on the previous page of this review). I did not review Protocols 0503, 0540 and 0541, primarily because the results of these protocols, which administered anakinra intravenously to healthy subjects, are not as pertinent to the labeling as the protocols noted above, plus I ran out of time to review.

The remaining 2 protocols submitted in this BLA were non-PK studies (Protocols 0560 and 980220). In these protocols, plasma anakinra levels were collected but a formal PK analysis was not performed. I briefly reviewed these protocols because they were conducted in the proposed population, subjects with RA.

1. Protocol 0501: Safety and pharmacokinetic study of human recombinant IL-1ra (ANTRIL) in patients with rheumatoid arthritis

Methods

This was a Phase 1, double-blind, single center, randomized, sequential single-dose escalation PK study of IL-1ra by SQ administration in male and female adult subjects with stable RA. The original IND sponsor, Synergen, conducted this protocol. Study dates: September to October, 1990. A non-polysorbate-80 formulation of IL-1ra was administered. The total sample size was 25 with 5 subjects in each of 5 arms (4 IL-1ra: 1 placebo). IL-1ra doses were 0.5, 1, 2, 4 and 6 mg/kg.

Blood sampling for PK was performed at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours postdose. IL-1ra levels were measured with ELISA. This assay does not distinguish between endogenous IL-1ra and anakinra. PK analysis was performed using standard noncompartmental methodology.

Results

Treatment groups were relatively comparable for age, race, gender and weight. There were no drop-outs.

A summary table of demographic and PK results for each dose level is located on page 2 , followed on page 3 by a graph of the mean (SD) plasma concentration for each dose level. In the graph, the low plasma anakinra levels for the placebo group suggest that endogenous levels will are not confound the PK assessment.

Exposure

The time to maximum plasma concentration (Tmax) fluctuated across dose levels, as did the Cmax. The area-under-the-plasma concentration-time-curve (AUC) increases in a relatively dose-proportional manner across the 0.5 to 4.0 mg/kg dose levels. Mean residence time (MRT) increased across the 1.0 to 4.0 mg/kg dose levels. The mean MRT_{SQ} for the 1.0 mg/kg SQ dose was 7.5 hr for the subjects with stable RA. Compared to a MRT_{IV} of only ~1.0 hr for healthy volunteers (reported by the sponsor in Protocol 0540), the MRT suggests that absorption is the rate-limiting step in the PK profile of anakinra (i.e., flip-flop kinetics).

Disposition

Apparent clearance (Cl/F) was relatively consistent across dose levels. Alternatively, the elimination half-life (t1/2) increased from 1.0 to 4.0 mg/kg.

Conclusions: The single-dose mean AUC increases in a dose-proportional manner from 0.5-4.0 mg/kg. The mean MRT suggests absorption-rate-limiting PK (i.e., flip-flop kinetics).

2. Protocol 0502: A single center, open-label, multiple dose safety and efficacy study of human recombinant interleukin-1 receptor antagonist in patients with rheumatoid arthritis

Methods

This was a Phase 1, open-label, single-center, sequential multiple-dose escalation PK study of IL-1ra by SQ administration in male and female adult subjects with active RA. The original IND sponsor, Synergen, conducted this protocol. Study dates: November, 1990 to April, 1991. The protocol does not state details about the formulation. The total sample size was 15 with 5 subjects in each of 3 arms. IL-1ra doses were:

Dose	Stage 1 Dose Duration	Washout	#1 Stage 2 Dose Duration	Postdose Assessment
2 mg/kg SQ daily	7 days	14 days	28 days	28 days
4 mg/kg SQ daily	7 days	14 days	28 days	28 days
4 mg/kg SQ BID	7 days	14 days	28 days	28 days

Blood sampling was performed at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours postdose on Days 1 and 7 of Stage 1 or 2. Urine samples were collected from 0- 12 hr postdose on Days 1 and 7 of Stage 1 only. IL-1ra plasma and urine levels were measured with ELISA (plasma LOQ — ng/mL; urine LOQ —ng/mL). PK analysis was performed using standard noncompartmental methodology.

Results

Due to the occurrence of injection site reactions during Stage 1 of the first 2 dose groups, the 4 mg/kg BID dose group was cancelled and these subjects were assigned to receive either 1 or 2 mg/kg for 28 days. In addition, only 2/5 subjects who received 4 mg/kg q day during Stage 1 went on to receive 4 mg/kg for 28 days during Stage 2. One of the 5 subjects dropped out prior to Stage 2, and the remaining 2 subjects received 1 mg/kg for 28 days. The summary table on page 5 demonstrates the final subject disposition.

Exposure

A summary table of the PK results from days 1 and 7 (either stage) for each dose group can be found on page 6. The mean Tmax increases with increasing dose for both days 1 and 7. The mean Cmax increases in a dose-proportional manner except between the 2 and 4 mg/kg dose groups on day 1. Mean AUC0-24 increases in a dose-proportional manner during day 1, and between the 1 and 2 mg/kg dose groups on day 7. However, the mean AUC0-24 for the 4 mg/kg dose group increased in a greater than dose-proportional manner. The mean AUC0-inf, calculated only for the day 1 data, shows concordance with the mean AUC0-24 for the 1 and 2 mg/kg but not the 4 mg/kg dose groups in terms of magnitude and direction. MRT was consistent between the 1 and 2 mg/kg dose groups but increased substantially for the 4 mg/kg dose group. The accumulation ratio (AR) for the lower dose groups is negligible but increases to a mean of 1.6 for the 4 mg/kg dose group.

Disposition

The mean apparent Cl increases between the 1 and 2 mg/kg dose groups and then reaches a plateau. This pattern, and the absolute values, were consistent for days 1 and 7. The mean terminal t1/2 on day 1 was similar for the 1.0 and 2.0 mg/kg dose groups but significantly shorter than for the 4.0 mg/kg dose group (4.1 hr). This, and the progressively increasing Tmax, is further evidence of the absorption-rate-limiting PK profile of anakinra. The mean (SD) plasma concentration-time graphs are located on page 7.

The results of the urine collection show negligible IL-1ra recovery. Given the molecular weight of IL-1ra, glomerular filtration is the most likely route of elimination. The lack of IL-1ra in the urine is consistent with the known amino acid conservation by the kidney tubules.

Conclusions: The mean Cmax and mean AUC increase in a dose-proportional manner from 1.0 to 4.0 mg/kg. The mean MRT results for Day 1 are consistent with the results from Protocol 0501; a flip-flop kinetic profile is seen. Minimal accumulation is seen after 7 days of dosing with 1.0 or 2.0 mg/kg SQ.

3. Protocol 100788: Population PK of anakinra in patients with rheumatoid arthritis

Methods

A population PK (PPK) analysis was conducted by the sponsor to increase the understanding of the SQ dose PK, and to explain the PK variability in male and female adult subjects with RA. Three studies (0501, 0502 and 0560) were included. A separate review of these protocols can be found on page 1, 4, and 30, respectively.

PPK analysis was performed using the nonlinear mixed-effects modeling method (NONMEM; version V, level 1.0, double precision, UCSF). The major criterion for model selection was the difference in the objective function values for 2 models. Initially, data from Protocols 0501 and 0502 were pooled and modeled. The resultant model was then used (with prior testing) to model the data from Protocol 0560. The 2-step modeling process was selected due to the significant discrepancy in sampling times in Protocol 0560 compared to Protocols 0501 and 0502. The pooled database was modeled separately for each week of the studies. Based on PK data from prior studies, a 1-compartment model with first-order absorption and elimination was used. The primary parameter was Cl/F. The fixed-effect parameters were Vd/F and Ka. The covariates were creatinine Cl (CrCl), age, body weight and sex. Bayesian estimates of the PK parameters for each subject were obtained.

Results

PPK Results for Protocols 0501 and 0502

Modeling results after the first step of the pooling process revealed that CrCl and body weight had a significant positive correlation with Cl/F, and that body weight was also a covariate for Vd/F. This is graphically represented on pages 10 and 11. A statistically significant impact of gender on Cl/F was also found, but this effect disappeared after adjustment for CrCl and body weight. Similarly, the mean Vd/F was greater in males compared to females however this effect disappeared after adjustment for body weight. A table that compares the PK parameters generated from the PPK model and from the original noncompartmental analysis is located below.

Mean (SD) anakinra PK parameters in subjects with RA (Studies 0501 and 0502)

Parameter	Study 0501	Study 0502	All
		Bayesian estimation	
n	20	15	35
Cl/F (mL/min)	96.5 (20.4)	116 (30)	105 (27)
Vd/F (L)	15.9 (10.3)	22.0 (12.1)	18.5 (11.3)
Ka (1/hr)	0.101 (0.032)	0.106 (0.036)	0.103 (0.033)
T1/2 (hr)	7.5 (2.5)	7.4 (3.1)	7.5 (2.7)
		Noncompartmental analysis	
Cl/F (mL/min)	101 (23)	121 (31)	
T1/2 (hr)	5.9 (3.0)	6.6 (4.0)	

PPK Parameter Values (Studies 0501 and 0502)

Intersubject Variability	CV%	95%CI
Cl/F	19.0	12.6-23.8
Vd/F	93.2	70.2-112
Ka	52.2	43.9-65.9
Residual Variability	**CV%**	**95%CI**
	25.5%	22.4-28.3

PPK Results for Protocol 0560

Results of sequential testing of the final model generated from the first pooling of data did not indicate a need to revise the model prior to analyzing the data from Protocol 0560.

Results of the PPK modeling of the data from Protocol 0560 was similar to that observed for Protocols 0501 and 0502. The Cl/F increased with increasing CrCl and body weight, and the Cl/F was greater in males than females. The Cl/F was also found to be greater in subjects <65 years old. After adjustment for CrCl and body weight, however, gender and age were not significant factors for Cl/F. The graphs on page 12 demonstrate these relationships.

The table below shows the Bayesian estimated PK parameters categorized by gender and age.

Mean (SD) Bayesian estimated anakinra PK parameters in subjects with RA (Protocol 0560)

	Age		Gender		All
Parameter	<65 yr	>65 yr	Males	Females	
N	262	79	79	262	341
Cl/F (mL/min)	152 (24)	138 (23)	164 (25)	144 (22)	149 (24)
Vd/F (L)	9.6 (2.2)	10.1 (2.3)	11.1 (2.2)	9.3 (2.1)	9.7 (2.2)
Ka (1/hr)	0.096 (0.024)	0.082 (0.021)	0.092 (0.021)	0.093 (0.025)	0.093 (0.024)
T1/2 (hr)	8.0 (1.9)	9.1 (2.1)	8.2 (1.8)	8.3 (2.1)	8.3 (2.0)

The overall mean Cl/F of 149 mL/min in Protocol 0560 is noticeably higher than the corresponding value of 105 mL/min found in Protocols 0501 and 0502. Since the subject characteristics were similar across all 3 protocols, the reason for the difference in Cl/F is unclear.

Inter- and intrasubject variability of Cl/F were 14.9% and 9.9%, respectively. The intersubject variability accounted for 69% of the total variability found in Cl/F.

Conclusions: Cl/F increased with increasing creatinine clearance and body weight. Gender and age were not significant factors for Cl/F after adjustment for creatinine clearance and body weight.

4. Protocol 970189: A double-blind, placebo-controlled, pharmacokinetic trial of continuous subcutaneous infusion of anakinra in patients with rheumatoid arthritis

Methods

This was a Phase 1, double-blind, placebo-controlled, randomized, sequential single-dose escalation PK study of a 96-hour continuous SQ infusion of IL-1ra in male and female adult subjects with stable RA. The protocol was conducted by Amgen. Study dates: August, 1997 to February, 1998. The TBM formulation was administered. This protocol was divided into 3 stages:

Stage	n (IL-1ra: placebo)	IL-1ra Doses (mg/kg/day)
1	20 (4:1)	0.6, 2
2		
cohort 1	10 (4:1)	2, 6
cohort 2	10 (4:1)	6
3	10 (4:1)	12

A — pump with a reservoir connected to an implanted SQ catheter was used to deliver IL-1ra (1 pump during Stages 1 and 2, and 2 pumps during Stage 3).

Blood sampling was performed at predose, 0.5, 1, 1.5, 2, 4, 8, and 12 hours on day 1, immediately prior to refilling the pump on days 2, 3 and 4, immediately prior to final pump removal on day 5, and at 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hr after final pump removal. IL-1ra levels were measured with ELISA with a LOD= — ng/mL. PK analysis was performed using standard noncompartmental methodology.

Results

The summary table on page 14 shows a generally dose proportional increase in the AUC0-t and AUC0-inf. A significant difference between the AUC0-t and AUC0-inf was not seen. The range for terminal t1/2 was — hr. The range for Cl/F was — mL/min with no consistent/obvious pattern of change between dose levels. As shown in the plasma concentration-time curves, steady state was achieved by 24 hr for all of the dose levels.

The sponsor performed an analysis to determine if concurrent administration of DMARD's (various types and combinations of DMARD's) had an effect on the terminal t1/2 or Cl/F. The results are shown on page 15: a difference was not seen in either case. However, the uncontrolled nature of this protocol with regards to DAMARD's use prevents the formation of useful conclusions. An analysis of Cl/F and baseline creatinine Cl did not reveal any relationship (see page 15 for the plot).

Conclusions: The mean AUC increased in a dose proportional manner across the dose range of 0.6 to 12 mg/kg/day as a 96-hour continuous SQ infusion. This finding is similar to the exposure profile seen with SQ bolus dose administration. Steady state plasma concentrations were achieved by 24 hours for all dose levels.

5. Protocol 0530: Bioavailability of two formulations of interleukin-1 receptor antagonist (rhIL-1ra): pharmacokinetic analysis

Methods

This was a Phase 1, single center, randomized, balanced, open-label, single-dose, three-treatment, three-period crossover study of IL-1ra in healthy male adult subjects. The protocol was conducted by then-IND sponsor, Synergen. The goal was to determine the bioavailability of the original and a new IL-1ra formulation compared to a 3-hr iv infusion of the original IL-1ra formulation. The new formulation was different due to the addition of [redacted] polysorbate-80, and a 70 mg/mL concentration of rhIL-1ra (versus 200 mg/mL for the original formulation). [redacted] Study dates: November 3-23, 1991. The total sample size was 12 with each subject receiving 3 treatments in a randomized manner:

Treatment A: 70 mg IL-1ra SQ (original formulation)
Treatment B: 70 mg IL-1ra via a 3 hr iv infusion (original formulation)
Treatment C: 70 mg IL-1ra SQ (new formulation)

Multiple blood sampling for PK was performed from predose to 24 hours postdose for each of the SQ and iv doses. IL-1ra levels were measured with ELISA (LOD= [redacted]/mL). PK analysis was performed using standard noncompartmental methodology.

Results

All but 1 subject (withdrew for personal reasons) completed the protocol; this subject received only Treatments A and B.

Original formulation: iv v. SQ route of administration

The summary tables on pages 17 and 18 indicate that the iv route of administration produced a larger exposure when measured by mean Cmax and by mean AUC compared to the SQ route. The mean (SD) plasma concentration-time curves on page 19 demonstrate these differences between the iv and SQ routes of administration. The mean $Cmax_{iv}$ was significantly higher compared to $Cmax_{SQ}$ but the SQ route leads to a longer MRT, and hence, a longer duration of a higher plasma concentration compared to the iv route. The prolonged MRT_{SQ} is evidence of the absorption-rate-limiting kinetics. The mean terminal t1/2 was significantly longer for the iv route.

SQ route: original v. new formulation

The summary table on page 18 indicates that the new formulation produced a statistically significantly greater exposure as measured by mean Cmax and mean AUC. No difference in Tmax was found. The larger mean AUC is most likely due to the statistically significantly greater mean bioavailability of the new formulation (95% v. 84% for the new and original formulation, respectively) although a difference in clearance may also impact the AUC. The mean terminal t1/2 for the new formulation is shorter than for the original formulation, but because of the flip-flop kinetics, this finding is actually indicative of the absorption rate. The faster absorption rate for the new formulation is consistent with its shorter mean MRT compared to the original formulation. The mean absorption time (MAT) provides further evidence for the faster rate of absorption for the new formulation.

Conclusions: When given as a 70 mg SQ injection (single dose), the TBM formulation has a greater extent (as noted by F) and a faster rate (as noted by the decrease in MRT and MAT) of absorption compared to the original formulation. This resulted in a statistically significantly greater exposure as measured by Cmax and AUC.

6. Protocol 0555: An open-label, single-dose study of the safety, PK and tolerability of recombinant-methionyl human interleukin-1 receptor antagonist (r-metHuIL-1ra) in chronic renal failure patients undergoing dialysis

Methods

This was a Phase 1, open-label, single dose PK study of IL-1ra by iv administration in male and female adult subjects with clinically-stable, chronic renal failure. The primary goals were to determine the PK of IL-1ra in subjects undergoing dialysis, and to determine the effect of hemodialysis (HD) or chronic ambulatory peritoneal dialysis (CAPD) on the PK profile. The protocol was conducted by then-IND sponsor, Synergen. Study dates: March 14 to May 16, 1994. The total sample size was 20 (10 subjects on HD, 10 subjects on CAPD). The IL-1ra dose was 1.0 mg/kg via iv bolus. The TBM formulation was used.

Blood sampling for PK was performed at predose, 0.5, 1, 2, 3, 6, 8, 10, 12, 24, 36, 48, 60, 72, and 96 hours postdose. For CAPD subjects, periodic sampling of the dialysate was performed predose and over the 96 hours postdose interval as the dialysis bag was changed. For subjects on HD, dialysate sampling was performed predose, and pre-, mid- and postdialysis (corresponds to 6, 8 and 10 hours postdose, respectively). A urine collection was performed for 96 hours postdose. Plasma. urine and dialysate IL-1ra levels were measured with the same ELISA (LOQ= — ng/mL for plasma and dialysate, — ng/mL for urine). PK parameters were calculated using standard compartmental analysis methods.

Result

Twenty subjects completed the protocol and were included in the PK analysis. The plasma IL-1ra level at 0.5 hours postdose for 2 subjects were deemed to be outliers (2.2-fold and 3.4-fold higher than the mean for that timepoint) and were excluded from the analysis.

The mean (SD) plasma concentration-time curves on page 21 show that the curve for the HD and CAPD subjects are essentially superimposable during the 96 hours after a single iv dose of IL-1ra in this non-RA subject population. The summary table of PK parameters, located on page 22, shows a similar profile.

Exposure

The exposure (as measured by mean Cmax, mean AUC0-inf and mean MRT) is nearly identical for the 2 groups of subjects.

Disposition

The disposition (as measured by mean t1/2 α, mean t1/2 β, and mean total clearance) is nearly identical for the 2 groups of subjects. A 2-compartmental decline in plasma IL-1ra concentration is seen. The mean renal clearance in the CAPD group was more than twice that in the HD group. This finding corresponds to the greater mean urinary recovery of IL-1ra in the CAPD group compared to the HD group (9.1 v. 4.1 %Dose, respectively; see the tables on page 23 and 24) however the CV% is very large for both groups. The mean initial distribution volumes of 3.13 and 2.99 L for the HD and CAPD groups, respectively, are consistent with intravascular volume. By steady-state, these mean distribution volumes expand somewhat to encompass the intravascular volume and extracellular fluid.

Conclusions: Subjects in the CAPD group had a greater mean renal clearance and urinary recovery of IL-1ra compared to subjects in the HD group. Otherwise, the exposure and disposition profiles of the 2 groups after a single iv bolus dose of 1.0 mg/kg were nearly identical.

APPEARS THIS WAY
ON ORIGINAL

7. Protocol 0563: An open-label, single-dose study of the safety, PK and tolerability of recombinant-methionyl human interleukin-1 receptor antagonist (r-metHuIL-1ra) in patients with hepatic dysfunction

Methods

This was a Phase 1, open-label, single-dose PK study of IL-1ra by iv administration in male and female adult subjects with wither clinically-stable hepatic dysfunction, or normal hepatic function. Only subjects with Child Class B hepatic dysfunction (total bilirubin of 2-3 mg/dL, albumin of 2.8-3.5 mg/dL, minimal hepatic encephalopathy, easily controlled ascites, or score of 9-11) were enrolled. The primary goals were to determine the PK of IL-1ra in subjects with either normal or impaired hepatic function, and compare the PK profiles of the 2 groups. The total sample size was 24 (12 subjects with hepatic dysfunction:12 subjects with normal hepatic function). The protocol was conducted by then-IND sponsor, Synergen. Study dates: May 16 to August 10, 1994. The IL-1ra dose was 1.0 mg/kg via iv bolus. The TBM formulation was used.

Blood sampling for PK was performed at predose, 1, 5, 15, 30, and 45 minutes, 1, 2, 3, 6, 8, 10, 12, 15, 18, 21, and 24 hours postdose. A urine collection was performed for 24 hours postdose. Plasma, and IL-1ra levels were measured with the same ELISA (LOQ= — ıg/mL for plasma — ng/mL for urine). PK parameters were calculated using standard compartmental analysis methods. Subjects were matched for sex, age and weight.

Results

For administrative reasons, the sponsor terminated the protocol after enrolling 12 subjects with hepatic dysfunction and just 2 subjects with normal hepatic function. The data are unaudited, and for this reason, I will only briefly address the results.

The plasma concentration-time curve, located on page 26, shows a tri-exponential decline for this subject population with mild-moderate hepatic dysfunction. The brief increase in plasma concentration seen at 6 hours postdose may be due to enterohepatic recycling. This pattern can be seen on other PK curves (see page 3) where the plasma levels were monitored more frequently during the first 6-12 hours postdose. In subjects with hepatic dysfunction, the plasma level is rapidly approaching zero by 24 hours postdose. As shown in the summary table on page 27, the mean terminal t1/2 is 3.44 hours and the mean total clearance is 95.1 mL/min.

The mean terminal t1/2 and mean total clearance are significantly different from the subjects on dialysis who were also given a single iv dose of 1 mg/kg (the mean terminal t1/2 is longer, and the mean total clearance is lower in the subjects with CRF; see review of Protocol 0555 on page 20). Not surprisingly, the Cmax and AUC0-inf is lower in this subject population compared to the dialysis subjects. Amgen performed a comparison of the PK profile of the 1 mg/kg iv dosing regimen in healthy subjects, subjects with CRF, and subjects with hepatic dysfunction. The review of this comparison is located on the next page.

The urine volume data at each collection were not available to the sponsor therefore urinary recovery was not calculated.

Conclusions: None. Please see the next page.

8. Comparison of anakinra PK from healthy subjects, subjects with CRF, and subjects with hepatic dysfunction

Methods

Amgen compared the PK data from Protocol 0555 (subjects with chronic renal failure [CRF]), Protocol 0563 (subjects with hepatic dysfunction), and Protocol 0540 (healthy subjects). The review of Protocol 0555 is located on page 20; the review of Protocol 0563 is located on page 25. After prioritizing the multiple protocols of this BLA, I decided to not review Protocol 0540, a single-dose study of the 1 mg/kg iv dose in 12 healthy male subjects.

Results

The plot located on page 29 shows that the plasma clearance of IL-1ra decreased as the estimated creatinine clearance decreased. The plasma clearance of IL-1ra was decreased 86% in the subjects with CRF, and was decreased 30% in the subjects with hepatic dysfunction, compared to that in healthy subjects. The variability in the plasma clearance data also increased in the subjects with CRF, and in particular, in the subjects with hepatic dysfunction. Compared to the healthy subjects, the mean terminal t1/2 was essentially unchanged in the subjects with hepatic dysfunction but was increased more than 2-fold in the subjects with CRF. The mean distribution volume at steady state was essentially unchanged across the 3 groups. Exposure, measured by MRT, was 8-times greater in the subjects with CRF.

Conclusions: For a 1.0 mg/kg iv bolus dose of IL-1ra, plasma clearance decreases as creatinine clearance decreases. In this study, the decrease in plasma clearance was associated with an increase in terminal t1/2 and an increase in exposure (by MRT).

The results of this study underscore that the primary route of elimination in humans is glomerular filtration. The subjects with CRF did not appear to have an increase in toxicity due to the increase in IL-1ra exposure. However, only a single dose of 1.0 mg/kg was administered (albeit administered iv, with the resultant 100% bioavailability and greater exposure compared to a SQ bolus). The safety and PK profiles of IL-1ra when administered as a daily SQ bolus in the CRF population are unknown and should be studied during Phase 4.

9. **Protocol 0560: A multicenter, double-blind, dose-ranging study of recombinant methionyl human IL-1ra (Anakinra) in patients with active rheumatoid arthritis**

Methods

This was a Phase 2, double-blind, multicenter (all in Europe), randomized, dose ranging study of IL-1ra by SQ administration in male and female adult subjects with active RA. IL-1ra plasma levels were measured as an adjunct to the primary goals of assessing the safety and efficacy. The total planned sample size was 520 (130/arm) IL-1ra

doses were 30, 75 and 150 mg SQ daily for 24 weeks. Study dates: May, 1994 to November, 1995. The TBM formulation was administered.

Blood sampling for IL-1ra plasma levels was performed at predose, and during weeks 1, 4, 12, 20 and 24. Actual timing of sampling was in the morning after the evening dose administration (typically 12 - 16 hr postdose). IL-1ra levels were measured with ELISA. PK analysis was not performed.

Results

The study was terminated after 473 enrolled subjects. Plasma levels were available and analyzed for 259 subjects. The sponsor used the geometric mean of the concentration because it provided a better measure of the central tendency.

The mean plasma concentration at 12-16 hr postdose during daily administration of anakinra increased in a dose-proportional manner, as demonstrated in the summary table on page 31. The mean plasma concentrations at 12-16 hrs postdose were 20-30% of the mean Cmax seen in Protocols 0501 and 0502. Evidence for accumulation was not found over the 24-week dosing period.

The sponsor's attempt to determine a dose-response relationship was impeded by the considerable overlap in plasma concentration across the 3 dose groups. This overlap is shown in the figure on page 32 where dose is presented as dose per kg body weight. The sponsor performed an exploratory analysis of the efficacy (measured by ACR20 and sustained ACR20), and of the reason for withdrawal in each dose per kg body weight group. This analysis demonstrated a greater sustained efficacy response in the 1- 1.5 mg/kg anakinra group compared to the remaining dose groups or placebo (see the table on page 32). The 1 - 1.5 mg/kg dose group also had a lower withdrawal rate than the >1.5 mg/kg dose group.

Conclusions: A dose proportional increase in the steady state mean plasma IL-1ra concentration was seen in the dosing regimen and range studied (30, 75, and 150 mg fixed-dose SQ daily). There was no evidence of accumulation. Analysis of the safety and efficacy data suggested that the 1.0 mg/kg dose level may be optimal.

10. Protocol 980220: A multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of a continuous subcutaneous infusion of anakinra (r-metHuIL-1ra) in patients with rheumatoid arthritis

Methods

This was a Phase 2, double-blind, multicenter, randomized, placebo-controlled study. A 24-week continuous SQ infusion of IL-1ra, at doses of 0.6, 4.0 or 9.0 mg/kg/day, was given to male and female adult subjects with stable RA. Study dates: November, 1998 to the present. The total sample size was 280 with 70 subjects per arm. The TBM formulation was used but was first enhanced specifically for continuous infusion delivery by the addition of —

—

Due to an unstable formulation, this protocol was halted after 21 subjects had been treated for 11 weeks. The sponsor notes that the instability was due to the temperature of the solution reaching 37 degrees for extended periods, and related this to the use of the — ump. To continue the safety monitoring of the subjects who were treated, and to continue providing subjects with IL-1ra, the protocol was amended to an open-label design that administered the unaltered (i.e., TBM) formulation at a daily SQ bolus dose of 2.0 mg/kg for 72 weeks to those subjects enrolled by a certain date. Seventeen subjects were enrolled in the SQ bolus protocol.

In the continuous infusion protocol, blood sampling for PK was performed at predose, and at 1, 2, 3, 4, 8, 12, 16, 20, 24 and 26 weeks. A PK assessment was not performed in the SQ bolus protocol. Information was not provided regarding the measurement of the IL-1ra levels or how the PK analysis was performed.

Results

Although PK data were collected, the clinical study report does not present the results. However, the Clinical Pharmacology Summary of the BLA (Item 6, Volume 1) briefly addresses the PK results from the continuous infusion portion of the study.

PK data from the continuous infusion portion of the study were available from 15 subjects, 12 of whom received IL-1ra. The dose that each subject received was not provided. Eight weeks of plasma samples were available for these subjects. The steady-state concentration was estimated as the average of the concentrations collected weekly.

A graph of the plasma levels v. dose is presented on page 34. There appears to be a linear relationship between dose and steady-state IL1-ra levels over the dose range studied.

Conclusions: There appears to be a linear relationship between dose and steady-state IL1-ra levels over the dose range studied. However, the sponsor does not presently intend to market this enhanced version of the TBM formulation, therefore the results of this study are not pertinent at this time.

11. Protocol 0503:

NOT REVIEWED DUE TO LACK OF TIME AND THE LESSER RELEVENCE OF THE STUDY RESULTS TO THE PROPOSED LABELING

12. Protocol 0540:

NOT REVIEWED DUE TO LACK OF TIME AND THE LESSER RELEVENCE OF THE STUDY RESULTS TO THE PROPOSED LABELING

13. Protocol 0541:

NOT REVIEWED DUE TO LACK OF TIME AND THE LESSER RELEVENCE OF THE STUDY RESULTS TO THE PROPOSED LABELING

Conclusions:

- Anakinra demonstrates dose proportional increases in exposure (area under the curve and maximum plasma concentration) during single- and multiple dosing in the 0.5 to 4.0 mg/kg dose range in subjects with RA.
- Minimal accumulation of anakinra is seen during 24 weeks of daily SQ bolus dosing with a dosing range of 30-150 mg as a fixed-dose.
- The PK profile of anakinra, when given SQ, is absorption-rate-limited in the dose range studied in this BLA (i.e., flip-flop kinetics).
- The apparent clearance of anakinra increases with increasing creatinine clearance and body weight. Gender and age were not significant factors for the apparent clearance, after adjustment for creatinine clearance and body weight.
- The pharmacokinetic profile of a single dose of 1.0 mg/kg administered iv is significantly altered in subjects with chronic renal failure. Plasma clearance of IL-1ra is decreased in subjects with chronic renal failure compared to that in healthy subjects. Exposure is greater in subjects with CRF. The safety and PK profiles of IL-1ra, when administered as a daily SQ bolus to subjects with chronic renal failure, are unknown and should be studied during Phase 4 in order to permit effective labeling for this patient population.
- A formal study to determine the potential for drug-drug interactions between methotrexate (or any other type of disease modifying anti-rheumatic drugs) and anakinra has not been conducted.