CLINICAL PHARMACOLOGY REVIEW of
BLA 98-0012, cA2

Sponsor: Centocor

Product: Chimeric (Human-Murine) Monoclonal Antibody to TNF, cA2

Indication: Inflammatory Bowel Disease

Introduction

cA2 is a human/murine chimeric monoclonal IgG1 directed against TNFα. The Mab binds and therefore inhibits the activity of TNFα which is important in the pathophysiological process of inflammatory disorders including Crohn's disease. cA2 is glycosylated and has a molecular weight of approximately 150, 000 daltons.

Four clinical trials were used to establish the pharmacokinetics of cA2. Trials C0168T08 and C0168T11 studied the pharmacokinetics of cA2 after doses of 1, 5, 10 or 20 mg/kg. The pharmacokinetics of [illegible] were investigated in studies C0168T20 and C0168T16.

List of Studies:
1. Phase I Study of Chimeric Monoclonal Anti-TNF Antibody (cA2) in Severe Crohn's Disease, C0168T08. Lots 92E12 and 93C01.

2. Phase II Multi-Center Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Active Crohn's Disease. C0168T11. Lots 93C01 and 94D02.

3. A Placebo-Controlled, Dose-ranging Study Followed by a Placebo-Controlled, Repeated Extension of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Active Crohn's Disease. C0168T16. Lots 94D02 and 94L02.

4. A Placebo-Controlled, Repeated-Dose Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Enterocutaneous Fistulae as a Complication of Crohn's Disease. C0168T20. Lot 95K06.

Review of Studies:
1. C0168T08 was an open, label, single infusion study of 10 mg/kg (N=8) and 20 mg/kg (N=2). Both males and female patients were studied. cA2 was infused approximately over a 2 to 3 hour period. Blood samples were taken for pharmacokinetics prior to infusion and at 5 min, 1, 2, 4, 8, 12, 24, and 72 hours after infusion; and 2, 4, 6, 8 weeks. The presence of HACA was determined prior to infusion and at 2, 4, 6, and 8 weeks; and 4, 5, and 6 months. Additionally, blood levels of TNFα, sTNFr, sIL-2r, IL-6 and complement were determined. B- and T-lymphocyte subpopulations were examined prior to infusion and at 1 and 24 hours after infusion; and at 4 and 8 weeks. Serum levels were assessed with an enzyme immune assay (EIA) method with a lower limit of quantitation of approximatley [illegible] Patients given 20 mg/kg were reported but not

statistically evaluated for their pharmacokinetics due to their small number (N=2).

Pharmacokinetic Endpoint	Median Value for Patient given cA2 10 mg/kg, N=7, except for Cmax where N=8
Cmax, ug/ml	211.0
AUCinf, ug-hr/ml	45762
Clt, ml/hr	15.6
Vdss, ml	5686
MRT, hrs	336
t1/2, hrs	357

Table of pharmacokinetics values for patients given 10 mg/kg cA2.

Pharmacokinetic Endpoint	Data for patients (N=2)given 20 mg/kg cA2
Cmax, ug/ml	587, 821
AUCinf, ug-hr/ml	347811, 119955
Clt, ml/hr	4.5, 9.0
Vdss, ml	2469, 5297
MRT, hrs	550, 588
t1/2, hrs	411, 537

Table of pharmacokinetics values for patients given 20 mg/kg cA2.

HACA formation was not observed in 7 of 8 patients. In 1 patient, HACA could not be evaluated due to serum interference.

2. Phase II Multi-Center Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Active Crohn's Disease. Study C0168T11

The immunigenicity and pharmacokinetics of a single dose of 1, 5, 10, or 20 mg/kg were determined in patients with Crohn's disease. The study was designed in 2 stages. Stage 1 is an open, label dose escalation study to identify a minimally effective dose as well as the highest dose without unacceptable toxicity. Stage 2 utilizes a dose from Stage 1 in a double-blind,

placebo-controlled study to assess safety and efficacy. Blood samples were obtained for pharmacokinetics prior to infusion and at 1, 2 and 4 hours; and weeks 2, 4, 8, and 12. HACA levels were evaluated from blood samples taken prior to dosing and weeks 2, 4, 8, and 12. Serum levels were assessed with an enzyme immune assay (EIA) method with a lower limit of detection of [redacted] cA2 was administered as a 3 hour infusion.

Pharmacokinetic Endpoint	1 mg/kg, N=5	5 mg/kg, N=5	10 mg/kg, N=5	20 mg/kg, N=5
Cmax, ug/ml	23	75	181	344
AUCinf, ug-hr/ml	3124	18913	48915	76103
Clt, ml/hr	22.4	20.2	16.9	13.2
Vdss, ml	4347	5753	5027	5095
MRT, hrs	193	286	295	396
t1/2, hrs	78	187	240	191

Table of cA2 pharmacokinetics C0168T11.

3. A Placebo-Controlled, Dose-ranging Study Followed by a Placebo-Controlled, Repeated Extension of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Active Crohn's Disease. Study C0168T16

The study is divided into 2 parts: an initial treatment phase [redacted] The initial treatment phase was a double-blind, 4-arm parallel study comparing placebo, 5, 10, and 20 mg/kg doses. [redacted] treatment of Crohn's disease a double-blind, placebo-controlled study. A dose of 10 mg/kg was used in the [redacted] phase. Both phases included as endpoints immunogenicity, pharmacokinetics, safety and tolerance.

Initially, 25 patients were to enter 1 of 4 single dose groups in phase 1. At week 4, patients not responding were offered an open-label treatment with 10 mg/kg. Patients with at least a 70-point decrease from baseline in their CDAI score at week 8 following their initial treatment were randomized to a placebo-controlled, double-blind, 2-arm parallel [redacted]

For the initial phase of the study, blood samples for pharmacokinetics were taken prior to

infusion, end of the 1st infusion and at 1, 2 and 4 hours post infusion (first infusion only); an additional samples were taken at weeks 2, 4, 8 and prior to the 5th infusion at week 12. In the placebo controlled, second phase of the study, blood sample for pharmacokinetics were taken prior to infusion at weeks

At week 36 samples were obtained not only before infusion but also at the end of infusion. Additionally, pharmacokinetics sampling was performed during weeks and Therefore, the pharmacokinetics sampling represents an initial infusion described by sampling over weeks 0 through 12 which is followed by trough levels from week 12 though 36 and followed as a decay curve from weeks The pharmacokinetics of cA2 were proportionate to dose for AUC and Cmax, and dose did not influence Clt or t1/2. Therefore, the pharmacokinetics of cA2 conformed to a first order system which did not exhibit saturation under the conditions of study.

Pharmacokinetic Endpoint	5 mg/kg, N=27	10 mg/kg, N=28	20 mg/kg, N= 28
Cmax, ug/ml	144 ± 67.9	299.5 ± 105.8	544.9 ± 222.8
AUCinf, ug-hr/ml	33218 ± 12513	83017 ± 56315	151294 ± 87076
Clt, ml/hr	10.9 ± 3.6	10.7 ± 4.0	11.5 ± 5.9
Vdss, ml	3223 ± 1242	3196 ± 1281	4308 ± 3004
MRT, hrs	313 ±128	356 ± 333	391 ± 192
t1/2, hrs	241 ± 111	324 ± 258	361 ± 155

Table of Mean and standard deviation of pharmacokinetic values after various doses of cA2 during phase 1.

Although the t1/2's were statistically different between the 3 doses of cA2 in study C0168T16, these findings are not likely to reflect true pharmacokinetic differences. Rather the differences reflect sampling errors as both Clt and Vdss remain unchanged.

During the open-label extension patients given either placebo, 5, 10 or 20 mg/kg were given 10 mg/kg and trough levels sampled at weeks 2, 4, 8 and 12. Residual levels of the 20 mg/kg dose influenced the blood levels of cA2 in patients given 10 mg/kg; otherwise, the influence of prior dosing with placebo, 5 or 10 mg/kg was not evident. With increasing time over weeks 2 through 12 the heightened levels due to the prior experience with 20 mg/kg decreased, so that by week 12 the contribution was relatively small. Blood levels of cA2 in patients given placebo, 5 or 10 mg/kg did not appear meaningfully different based on the reported range of blood levels, although no statistical tests were performed to specifically address this issue.

Patients given during the second phase demonstrated pharmacokinetics comparable to the pharmacokinetics obtained in the initial treatment phase. No evidence of up- or down-regulation as an induction phenomenon was evident.

Infusion number	Placebo	10 mg/kg
1	36	37
2	30	32
3	25	31
4	22	27

Table of numbers of patients given infusions of cA2

4. A Placebo-Controlled, Repeated-Dose Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Enterocutaneous Fistulae as a Complication of Crohn's Disease. Lot 95K06 for cA2 and 95L14 for placebo. C0168T20.

C0168T20 was a double-blind, placebo-controleed, multicenter study in which Crohn's patients were given a dose of either placebo (N=32), 5 mg/kg (N=31), 10 mg/kg (N=31). Three treatment groups were dosed at weeks 0, 2, and 6. Each group was composed of approximately patients with draining enterocutaneous fistulae. The duration of infusions ranged from 1.0 to 2.6 hours, with the exception of one 5 mg/kg infusion of 0.5 hour.

Blood samples for pharmacokinetics were collected before and after each infusion at weeks 0, 2 and 6; and weeks 10, 14, 18, 26 and 34.

Plasma levels of cA2 appeared proportionate to dose and no accumulative effects of repeated administration were observed as illustrated in the table below.

	dose cA2	
Time period	5 mg/kg	10 mg/kg
1st infusion (week 0) - end	168	359
2nd infusion (week 2) - pre-infusion	34	75
2nd infusion (week 2) - end infusion	195	399
3rd infusion (week 6) - pre-infusion	22	51
3rd infusion (week 6) - end	178	427
post dosing week 10	23	68
post dosing week 14	5.4	18
post dosing week 18	1.4	5
post dosing weeks 26 and 34	<0.1	<0.1

Table of serum cA2 levels in patients with Crohn's disease.

A combined analysis of single infusion studies were conducted by pooling the results of studies C0168T08, C0168T11 and C0168T16. Cmax and AUC were proportionate to dose and no changes which were dependent on dose occurred in Clt or Vdss. However, Clt and Vdss were found to vary among the studies. Clt was found to be relatively high in study C0168T11 as compared to study C0168T16. Various possible sources for this difference were sought. A statistically significant gender difference ($p=0.005$) emerged from the data, but is not of biological significance with median values of 58 ml/hr for males and 55 for females.

A subgroup analysis of study C0168T16 was performed to examine some of the issues raised by the combined analysis. No significant relationships were observed between Clt and Vdss to gender, age or weight. A significant negative correlation was found between SGOT and Clt, but was not proportionate to SGOT levels. No influence of creatinine was observed on Clt or Vdss. Thus, eliminate of cA2 does not appear to be influenced by renal or hepatic function within the group of patients which were studied to date. When the effect of concomitant drugs on Clt or Vdss was examined, a statistically significant change in Vdss was observed for corticosteriods. The Vdss was found to change from a median value of 3277 ml for patients using corticosteriods as compared to 2811 for those not using steroids. The difference may result from changes in fluid balance know to occur with the use of corticosteriods. No differences in blood levels of cA2 were found between responders and non-responders in study C0168T16 at any dose (5, 10 or 20 mg/kg). A responder was defined as someone with a CDAI reduction of $\geq$ 70 points.

The effect of HACA on cA2 pharmacokinetics after a single dose infusion was examined by

pooling the results of studies C0168T08 and C01 8T11 and the initial phase of study C0168T16. Pharmacokinetic endpoints were compared using 31 HACA negative and 8 HACA positive patients. Although the Vdss was not found to be different between the groups, AUC/dose, Clt, MRT and t1/2 were different as illustrated below.

Pharmacokinetic Endpoint	HACA positive, N=8	HACA negative, N=31
AUC/dose, kg-hr/ml	3.1	4.4
Clt, ml/hr	19.8	15.7
Vdss, ml	3865	4014
MRT, hr	191	254
t1/2, hr	101	192

Table of Median pharmacokinetic values for patients with and without HACA.

The development of HACA was noted to have a detectable effect on blood levels of cA2 by 4 weeks post infusion.

A normal volunteer study was conducted in a European study which was not conducted under IND. Thirty-nine individuals were given cA2 in conjunction with endotoxin challenge. The pharmacokinetics data was reported as follows. In the 1.0 mg/kg group Cmax ranged from 16.5 ug/ml to in the 10 mg/kg group 269.8 ug/ml. AUC ranged from 3232.9 ug-hr/ml in the 1.0 mg/kg group to 37621.3 ug/kg group. HACA was observed in 16 of 32 evaluable subjects; no proportionate increase in HACA was observed corresponding with an increase in dose.

Comment: The difference between t1/2 as measured in the two single dose study, is more likely due to the problem of estimating t1/2 than a real difference in response between the two studies.

Conclusions:

1. At doses up to 20 mg/kg, Cmax and AUC were proportionate to dose and no effect was observed on either Clt (total body clearance) or Vdss (volume of distribution at steady state).

2. Elimination of cA2 is not influenced by changes in hepatic or renal function is the patient population studied.

3. Corticosteriods increased the Vdss from 2811 ml in patients without this concomitant medication to 3277 ml; this change is not likely to be medically meaningful and probably is due to fluid retention.

4. No pharmacokinetic differences were found between cA2 responders and non-responders.

5. The formation of HACA influenced AUC normalized by dose (AUC/Dose), Clt, and t1/2; however, these changes were not sufficiently large to influence dosing and do not appear to be clinically meaningful.

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