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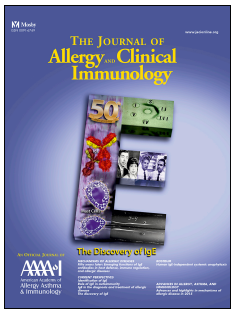

Catabolism of C1 inhibitor influences the response to replacement therapy in hereditary angioedema

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LETTER TO THE EDITOR

Catabolism of C1 inhibitor influences the response to replacement therapy in hereditary angioedema

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SUMMARY

Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is a disabling and life-threatening disease for which plasma-derived C1 inhibitor (pdC1-INH) is an effective treatment. Poor responses to pdC1-INH are rare. The aim of this prospective study was to evaluate the pharmacokinetics and pharmacodynamics of C1 inhibitor (C1-INH) in a C1-INH-HAE patient with poor response to treatment to investigate the mechanism underlying poor response to pdC1-INH. Seventeen C1-INH-HAE patients with normal responses to treatment served as retrospective controls. In the poor response patient, higher than standard doses of pdC1-INH did not change the PK but led to normalization of PD parameters and symptoms disappeared, recurring upon dose reduction. Therefore, we conclude that hyperactivation of the complement and contact systems in highly symptomatic C1-INH-HAE patients does not account for interpatient variability in response to pdC1-INH, which may be connected to differences in hepatic clearance of infused pdC1-INH.

CAPSULE SUMMARY

Pharmacokinetic data in a patient with poor treatment response to plasma-derived C1 inhibitor compared with 17 control patients suggest that poor treatment response likely depends on increased catabolism, but not through interaction with target proteases.

KEY WORDS

hereditary angioedema, C1 inhibitor, complement, contact system, pharmacokinetic, protein catabolism

ABBREVIATIONS

AUC_τ	area under the concentration-time curve at dosing interval τ
C1-INH	C1 inhibitor
C1-INH-HAE	Hereditary angioedema due to C1 inhibitor deficiency
CL	apparent total plasma clearance
C_{ss}	concentration at steady-state
HK	high-molecular-weight kininogen
PD	pharmacodynamics(s)
pdC1-INH	plasma-derived C1 inhibitor
PK	pharmacokinetic(s)
r	Pearson correlation coefficient
$T_{1/2}$	elimination half-life
τ	dosing interval
Vd	apparent volume of distribution

To the Editor,

Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is characterized by recurrent swelling attacks, mediated by bradykinin which is released upon activation of the contact system in patients lacking C1 inhibitor (C1-INH) (1). Replacement therapy with intravenous plasma-derived C1-INH (pdC1-INH) aims at restoring control of bradykinin release by maintaining protective C1-INH activity trough levels (2). Approved doses of pdC1-INH, 1000 IU twice weekly for prophylaxis (3), are generally effective but can fail in some patients with severe C1-INH-HAE (4).

This prospective, single-center, open-label study was designed to assess whether catabolism of C1-INH influences the response to pdC1-INH therapy in poor-response patients with severe C1-INH-HAE. Pharmacokinetic (PK) and pharmacodynamic (PD) parameters were evaluated before and after repetitive administration of high pdC1-INH doses (Berinert, CSL Behring). During the loading period, daily 3000 IU pdC1-INH infusions were repeated until 24-h post-infusion functional C1-INH levels exceeded 70% of normal. In the maintainance period, 3000 IU were administered 3-times weekly for 5 weeks, followed by 2000 IU twice weekly for 3 weeks. Adverse events, vital signs, and concomitant medications were monitored, revealing no safety findings of note.

One poor-response patient was enrolled; a 75-year-old woman with C1-INH-HAE due to a c.1475T>A (p.Met492Lys) mutation. She experienced up to 100 attacks annually. On-demand pdC1-INH and icatibant provided only limited benefit, prophylaxis with pdC1-INH, tranexamic acid, and danazol remained ineffective. At the time of the study, she received on-demand pdC1-INH or icatibant up to twice weekly.

Seventeen C1-INH-HAE patients with normal responses to pdC1-INH served as retrospective controls, providing blood samples obtained before and after 20 attacks that were treated with pdC1-INH (Berinert, CSL Behring).

Laboratory measurements were performed as previously described (5, 6). Functional and antigenic C1-INH concentrations were best fitted by 1-compartment models. P-Pharm population PK modeling software was used (version 3, Simed). For the poor-response patient, the elimination half-life was derived from estimated PK parameters ($T_{1/2}$=0.693*apparent volume of distribution[VD]/total plasma clearance[CL]). The area under the concentration-time curve during a dosing interval τ (AUC_τ) was estimated by the trapezoidal rule. The average plasma concentration at steady-state (C_{ss}) during τ was

calculated as AUC_τ/τ. Statistical analyses were performed using STATA software (version 13, Stata Corporation). Quantitative data were summarized as mean, standard deviation, and coefficient of variation. Relationships between quantitative variables were analyzed with the Pearson correlation coefficient (r). Comparisons between patients were made using a 1-sample t-test.

The study was conducted in accordance with the Helsinki Declarations and approved by the local Independent Ethics Committee (Ospedale Luigi Sacco, Milan). Written informed consent was obtained from the poor-response patient. The control patients had given written consent for their samples to be used for research purposes.

The poor-response patient had pre-infusion levels of functional C1-INH, C4, and C1q below detection limits, 25% of normal for antigenic C1-INH, and 60% for cleaved high-molecular-weight kininogen (HK). After 3 days with 3000 IU pdC1-INH, the maintenance period could start.

During 5 weeks with 3000 IU 3-times weekly, mean pre-infusion functional and antigenic C1-INH levels were 46% and 57% of normal, respectively, increasing to 86% and 53% post-infusion (Table I). C4 and C1q and cleaved HK reached the normal ranges on Days 4 and 2 and remained there (Figure 1). The patient took additional on-demand icatibant once.

During 3 weeks with 2000 IU twice weekly, mean pre-infusion functional and antigenic C1-INH levels were 18% and 30% of normal, increased to 53% and 71% post-infusion (Table I), but decreased rapidly thereafter (Online Repository, Figure 1). C1q remained within the normal range, C4 decreased to below 60% of normal, and HK remained above 40% (Figure 1). The patient experienced 5 attacks treated with icatibant and 1 without additional treatment.

Functional and antigenic C1-INH levels estimated for the poor-response patient from population PK models correlated well with the observed levels (r=0.85; p<0.001 and r=0.87; p<0.001, respectively). At steady-state, 9000 IU pdC1-INH weekly were estimated to result in average weekly systemic exposures (AUC) of functional and antigenic C1-INH of 11487 h.% (dose/CL) and 12941 h.%, respectively, and average C_{ss} of 68.4% (AUC/168 h) and 77.1% (Online Repository, Figure 1). 4000 IU weekly were estimated to result in average AUC of 5833 h.% and 7329 h.% and average C_{ss} of 34.6% and 43.1%. Apparent total plasma clearance (CL) of antigenic C1-INH was estimated at 0.51 IU/(h.%), Vd at 25.4 IU/%, and $T_{1/2}$ at 34.3 h. Estimated CL of functional C1-INH was significantly lower for the control patients than for the poor-response patient (0.37 vs. 0.56 IU/[h.%], p=0.002); Vd showed no significant difference (35.0 vs. 27.3 IU/%, p=0.19).

Plasma recovery of C1-INH after infusion of pdC1-INH was lower and clearance faster in our poor-response patient than in normal responders. She had no evidence of autoimmune or other disease and normal transaminase plasma levels. Concurrently with the worsening of symptoms, she had depletion of C4 and C1q and massive HK cleavage, indicating a profound degree of instability in the complement and contact systems. With high doses of pdC1-INH, PD parameters normalized and symptoms disappeared, recurring upon dose reduction. At either dose, PK parameters were consistent, with similar percentages of protein cleared from plasma.

In some patients with acquired C1-INH deficiency, symptoms are induced by autoantibodies that consume C1-INH (7). In our poor-response patient, however, no C1-INH antibodies were detected.

Other physiologic pathways of C1-INH catabolism include interaction with target proteases or binding to hepatic asialoglycoprotein receptors (8).

In our poor-response patient, high doses of pdC1-INH apparently normalized PD parameters and controlled clinical symptoms without changing the PK, suggesting that clearance of C1-INH was not dependent on the catabolic pathways provided by protease-inhibitor interaction.

Therefore, changes in the expression of hepatic asialoglycoprotein receptors, related to still undefined circumstances, could explain increased C1-INH clearance in our poor-response patient. Cirrhosis, often accompanied by increased expression of asialoglycoprotein receptors (9), was excluded.

We conclude that differences in treatment response to pdC1-INH replacement therapy may be connected to differences in hepatic clearance of the infused C1-INH protein rather than hyperactivation of the complement and contact systems in highly symptomatic C1-INH-HAE patients.

Sincerely,

Marco Cicardi M.D., Andrea Zanichelli M.D., Chiara Suffritti Ph.D., and Maddalena A. Wu M.D., Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milan and ASST Fatebenefratelli Sacco, Milan, Italy; Thomas Machnig M.D., CSL Behring, Marburg, Germany; Annalisa De Silvestri M.D., Clinical Epidemiology and Biometric Unit - Foundation IRCCS Policlinico San Matteo, Pavia, Italy; Mario Regazzi Pharm.D., Clinical and Experimental Pharmacokinetics Unit - Foundation IRCCS Policlinico San Matteo, Pavia, Italy; Carmine Tinelli M.D., Clinical Epidemiology and Biometric Unit - Foundation IRCCS Policlinico San Matteo, Pavia, Italy

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153 **FIGURE LEGENDS**

154

155 Figure 1: C1q, C4, and cleaved HK levels during the study in the poor-response patient with C1-INH-
156 HAE.

157 Normal levels (expressed as % of normal plasma levels in healthy subjects, mean values and 95%
158 confidence intervals) are 98.6% (97.6% to 99.6%) for C1q, 96.7% (91.7% to 101.6%) for C4, and ≤ 30%
159 for HK.

160 Abbreviations: C1-INH-HAE = hereditary angioedema due to C1 inhibitor deficiency; HK = high-
161 molecular-weight kininogen.

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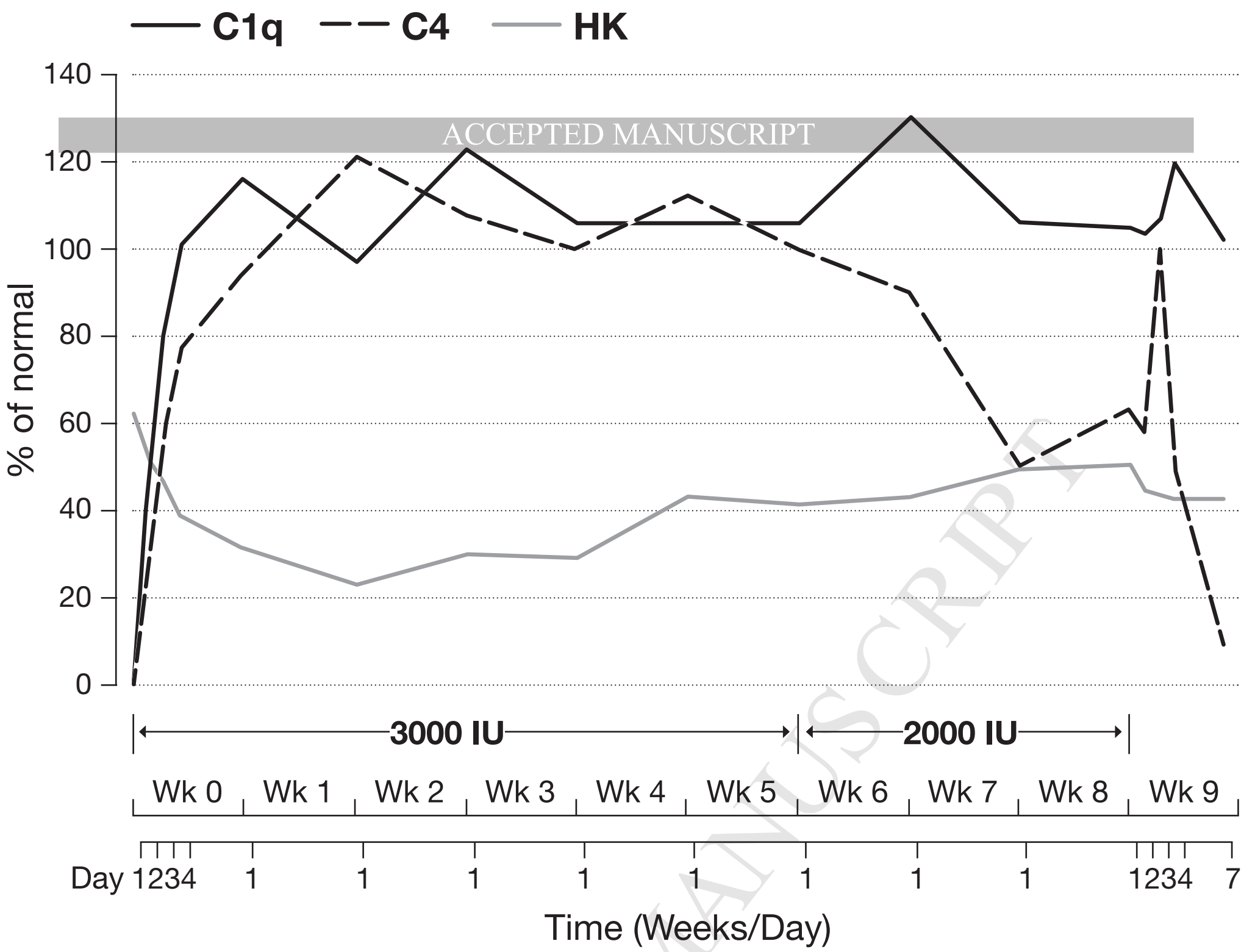
TABLES

Table I: Functional and antigenic C1-INH concentrations in the poor-response patient during the maintenance period

	Mean concentration in % (SD; CV)	
	Pre-infusion	Post-infusion, 10 min after end of infusion
Functional C1-INH		
9000 IU/week (3000 IU, 3 times weekly)	46 (30; 66)	86 (27; 31)
4000 IU/week (2000 IU, twice weekly)	18 (10; 59)	53 (10; 20)
Antigenic C1-INH		
9000 IU/week (3000 IU, 3 times weekly)	57 (23; 40)	112 (23; 21)
4000 IU/week (2000 IU, twice weekly)	30 (12; 42)	71 (15; 22)

C1-INH = C1 inhibitor; CV = coefficient of variation; SD = standard deviation.



ONLINE REPOSITORY

Figure 1: Observed and predicted concentrations of functional and antigenic C1-INH activities in the poor-response patient with C1-INH-HAE.

Observed (○) and predicted (solid lines) concentrations of functional (panel A) and antigenic (panel B) C1-INH activities (expressed as % of normal activity in healthy subjects). Normal functional and antigenic C1-INH levels ranged from 65% to 146% and 68% to 115%, respectively.

Abbreviations: τ = dosing interval; AUC = area under the concentration-time curve; C1-INH = C1 inhibitor; CL = apparent total plasma clearance; Css = concentration at steady-state; CV% = coefficient of variation; T1/2 = elimination half-life; Vd = apparent volume of distribution.

A. Functional C1-INH

Dose: 9000 IU (3000 IU, 3 times/week)

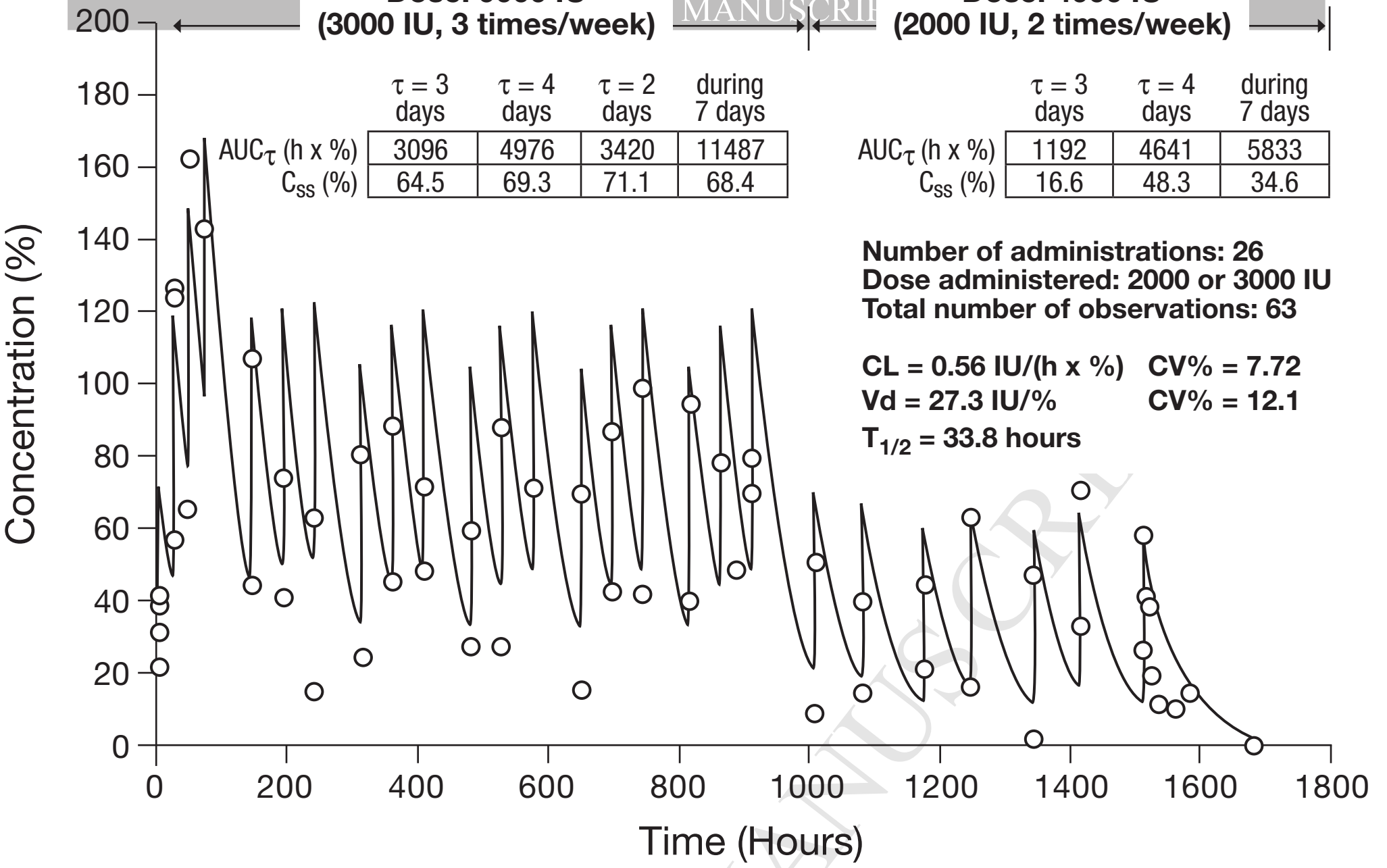
	τ = 3 days	τ = 4 days	τ = 2 days	during 7 days
AUC_τ (h x %)	3096	4976	3420	11487
C_{ss} (%)	64.5	69.3	71.1	68.4

Dose: 4000 IU (2000 IU, 2 times/week)

	τ = 3 days	τ = 4 days	during 7 days
AUC_τ (h x %)	1192	4641	5833
C_{ss} (%)	16.6	48.3	34.6

Number of administrations: 26
Dose administered: 2000 or 3000 IU
Total number of observations: 63

CL = 0.56 IU/(h x %) **CV% = 7.72**
Vd = 27.3 IU/% **CV% = 12.1**
$T_{1/2}$ = 33.8 hours



B. Antigenic C1-INH

Dose: 9000 IU (3000 IU, 3 times/week)

	τ = 3 days	τ = 4 days	τ = 2 days	during 7 days
AUC_τ (h x %)	3821	6328	3791	12941
C_{ss} (%)	79.6	74.0	79.0	77.1

Dose: 4000 IU (2000 IU, 2 times/week)

	τ = 3 days	τ = 4 days	during 7 days
AUC_τ (h x %)	2391	4848	7329
C_{ss} (%)	33.2	50.5	43.1

Number of administrations: 26
Dose administered: 2000 or 3000 IU
Total number of observations: 64

CL = 0.51 IU/(h x %) **CV% = 7.02**
Vd = 25.4 IU/% **CV% = 1.06**
$T_{1/2}$ = 34.3 hours