

Clinical Commentary Review

C1 Inhibitor Activity and Angioedema Attacks in Patients with Hereditary Angioedema

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Hereditary angioedema (HAE) is caused by deficiency or dysfunction in the C1 inhibitor (C1-INH) protein. C1-INH replacement therapy is used to treat patients with HAE to restore the missing or dysfunctional protein. *In vitro* studies showed that C1-INH inhibits prekallikrein activation and bradykinin formation in a dose-dependent manner when added to the plasma of patients with HAE. HAE is highly variable in clinical presentation, and early studies suggested that there was not a clear relationship between functional C1-INH levels and disease activity. Later, a threshold of approximately 40% functional C1-INH was identified, above which patients' risk of an attack was diminished. Long-term prophylaxis with plasma-derived C1-INH effectively reduces attack frequency and severity. Pharmacokinetic modeling shows that functional C1-INH levels are associated with the relative risk of having an attack. Subcutaneous administration of C1-INH results in consistently high levels of functional C1-INH activity, whereas intravenous administration results in periods of low trough functional C1-INH activity before the next scheduled dose, increasing the risk of an angioedema attack. These studies suggest that measurement of functional C1-INH activity may be useful as a biomarker of the risk of an attack in patients with HAE who are receiving long-term prophylaxis with plasma-derived C1-INH. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Hereditary angioedema; C1-inhibitor; Long-term prophylaxis; Pharmacokinetics

INTRODUCTION

Hereditary angioedema (HAE) with C1 inhibitor (C1-INH) deficiency is a rare condition in which patients have frequent, unpredictable attacks of nonpruritic submucosal or subcutaneous swelling. Abdominal and genitourinary attacks can cause severe pain and discomfort. Attacks that involve extremities can cause

disability, and attacks that involve the airway can be life-threatening. Pain and disability caused by HAE impairs quality of life and leads to depression and anxiety.¹⁻⁴ Patients have anxiety about future attacks and passing the condition to their children.^{1,3}

HAE is caused by mutations in the *SERPING1* gene, which produce deficient (type 1) or dysfunctional (type 2) C1-INH protein. C1-INH replacement therapy has been used to treat patients with HAE for almost 4 decades. C1-INH concentrate is administered on-demand at the beginning of an attack to reduce its duration and severity^{5,6} and at regular intervals as long-term prophylaxis to prevent attacks from occurring.^{7,8} The use of C1-INH concentrate to treat an attack in a patient with HAE was first described in 1973.⁹ The first plasma-derived C1-INH product was approved by regulatory authorities in Germany in 1979. The use of C1-INH replacement therapy to prevent attacks was first described in 1989.¹⁰

The goal of prophylaxis therapy with C1-INH is to prevent attacks by restoring normal C1-INH function. But what is the optimal dose of C1-INH for the prevention of attacks? Early studies of the management of patients with HAE suggested that there was no clear relationship between C1-INH levels and disease severity.¹¹ Later, a threshold of approximately 40% functional C1-INH was identified,¹² above which patients' risk of an attack was lower. Subsequent studies of C1-INH replacement therapy have used this threshold as a pharmacokinetic target,^{13,14} a minimum functional C1-INH level that should be maintained during prophylaxis treatment.

Here, we review the role of C1-INH in the pathogenesis of HAE, describe the rationale for therapeutic targets of functional C1-INH, and assess the implications of recently published clinical trial data that improve our understanding of the role of functional C1-INH activity in the treatment of patients with HAE.

ROLE OF C1-INH IN DISEASE PATHOGENESIS

The hereditary nature of HAE was first described by Osler in 1888.¹⁵ However, the recognition of the condition as a deficiency in C1-INH was not discovered until 1963 by Donaldson and Evans.¹⁶ Even then, the mechanism by which the angioedema events developed in these patients was not known. After initial suspicion that the mediator of swelling came from complement,¹⁷ subsequent work revealed and confirmed that bradykinin causes the vasodilation and leakage during angioedema attacks.¹⁸⁻²¹ Therefore, the bradykinin forming enzymes resulting from "contact activation" is central to the pathogenesis of angioedema attacks in patients with HAE (Figure 1).

C1-INH was named for its role in complement inhibition, but it is the only known plasma inhibitor of activated factor XII (factor XIIa) and it is the primary inhibitor of plasma kallikrein.

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Abbreviations used

C1 inhibitor- C1-INH

factor XIIa- activated factor XII

HAE- hereditary angioedema

Therefore, C1-INH is the most important inhibitory protein in the plasma kinin-forming cascade and is a major factor in the regulation of bradykinin. Low functional C1-INH causes the plasma of patients with HAE to be unstable, resulting in excess activation of factor XII, conversion of prekallikrein to kallikrein, and cleavage of bradykinin from high-molecular-weight kininogen (Figure 1). *In vitro*, prekallikrein that is bound to high-molecular-weight kininogen converts to kallikrein in the plasma of patients with HAE even without an initiating stimulus.²²

Although initial autoactivation of factor XII is a slow process, its rate increases over time as more factor XII is activated. However, even a small quantity of factor XIIa converts prekallikrein to kallikrein, and the kallikrein then rapidly activates the remaining factor XII, resulting in a positive feedback loop. Bradykinin is formed by the digestion of high-molecular-weight kininogen by kallikrein. Additional cleavage of factor XIIa by kallikrein produces a fragment called factor XIIIf or β -factor XIIa, which can also convert prekallikrein to kallikrein. Factor XIIIf also activates the C1r subcomponent of complement (which is not a function of factor XIIa) and leads to the cleavage of C4 and C2.

In the classical complement pathway, C1-INH inhibits the activation of C1 and the subsequent digestion of C4 and C2. Thus, when C1-INH functional activity is insufficient, a small amount of activated C1 is always present. Because C4 is the more sensitive substrate, C4 is depleted in most patients with

C1-INH-HAE,²³ even when they are feeling well. C1-INH also inhibits components of the lectin complement pathway, which might be involved in the pathogenesis of HAE. The mannose-binding lectin-associated serine protein-1 has been shown to cleave high-molecular-weight kininogen independently of kallikrein,²⁴ and C1-INH inhibits this reaction. In patients with HAE, mannose-binding lectin-associated serine protein-1 protein levels correlated with C1-INH functional activity and C4 antigen levels and negatively correlated with disease severity.²⁵ In the fibrinolytic system, plasmin activates factor XII (about 5%-10% as effectively as plasma kallikrein)²⁶ and degrades C1-INH. The latter effect may contribute to low C1-INH levels in patients with HAE,²⁷ particularly during periods of trauma or infection. Thus, although the bradykinin-forming reactions are primarily involved in the pathogenesis of swelling in patients with HAE, the implications of C1-INH deficiency are also relevant in the classical complement, lectin, and fibrinolytic pathways.

Addition of C1-INH to the plasma of patients with HAE *in vitro* restores stability and reverses all *in vitro* abnormalities in the bradykinin-forming cascade.²⁸ When C1-INH functional activity is insufficient, prekallikrein that is bound to high-molecular-weight kininogen is activated seemingly spontaneously even without a trigger (Figure 2). Addition of C1-INH inhibits prekallikrein activation in a dose-dependent manner. With small concentrations (<40 $\mu\text{g/mL}$, ~20% of the normal concentration *in vivo*), activation proceeds almost immediately. As the concentration increases (between 40 and 100 $\mu\text{g/mL}$, ~20%-50% of the normal concentration *in vivo*), activation is considerably slower. Thus, the complex of prekallikrein-HK with plasma is stabilized by the addition of C1-INH in a linear, concentration-dependent manner. The complex autoactivates if the level of functional C1-INH is inadequate. This activation occurs even if factor XII is not present.²⁹

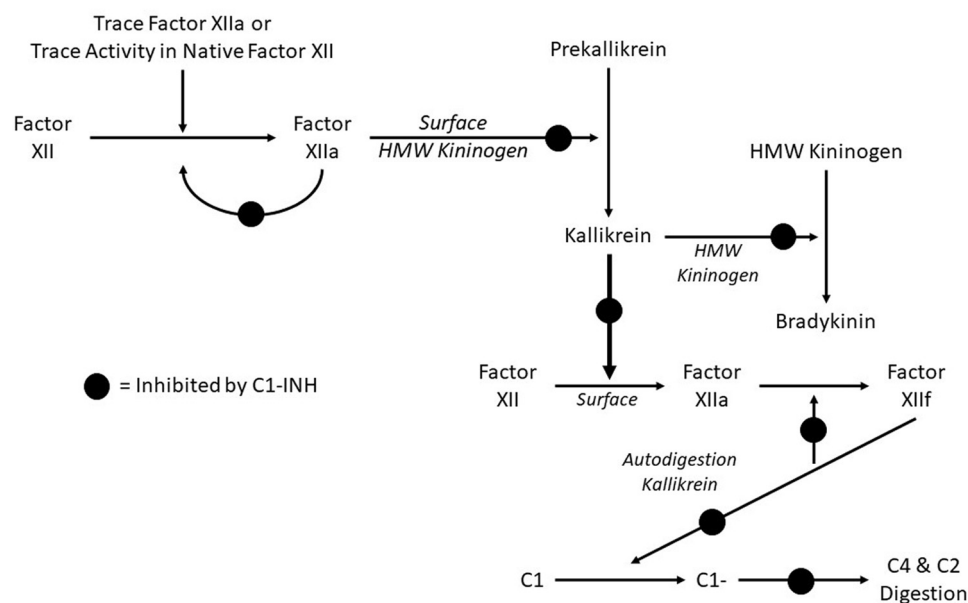


FIGURE 1. Schematic diagram of bradykinin formation in the contact system and the role of C1-INH inhibition. In the absence of C1-INH, factor XII is activated, causing the conversion of prekallikrein to kallikrein and the cleavage of bradykinin from high-molecular-weight (HMW) kininogen. Reprinted with permission from Kaplan and Joseph.⁵⁸

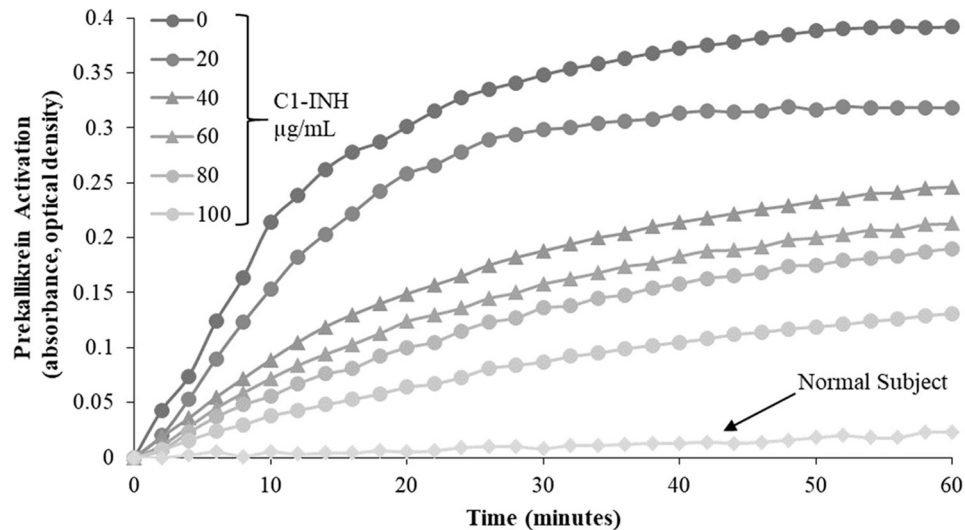


FIGURE 2. *In vitro* prekallikrein activation in plasma from a patient with HAE with added plasma-derived C1-INH at various concentrations compared with plasma from a normal subject. (Reprinted with permission from Kaplan and Maas⁵¹).

Patients with HAE are heterozygotes with 1 functional and 1 mutated *SERPING1* gene. Therefore, they could theoretically produce approximately half the functional C1-INH a healthy individual with 2 functioning genes produces. However, functional C1-INH levels in untreated patients with HAE are typically less than half of those in healthy individuals, and patients with HAE also catabolize C1-INH more rapidly than do healthy individuals.³⁰ The reasons for this phenomenon are not fully understood. One potential explanation is that C1-INH is an “activatable inhibitor.” When it binds to an enzyme, the target cleaves the C1-INH molecule, and the cleaved C1-INH binds to the active site of the enzyme. Thus, the target enzyme is irreversibly inhibited, and the bound C1-INH molecule is not capable of targeting an additional enzyme molecule. Another potential explanation is that messenger RNA of the abnormal allele inhibits the translation of the normal allele, a process called transinhibition.³¹ This process may also occur at the protein level. A recent study showed that in a subset of patients with certain mutations in the *SERPING1* gene, normal and mutant C1-INH proteins aggregated and were trapped in the endoplasmic reticulum, preventing the release of the functional C1-INH protein produced from the normal copy of the gene.³² Finally, other mechanisms unrelated to protease interactions or transinhibition may be involved, such as increased hepatic clearance.³³ Thus, multiple mechanisms may affect functional C1-INH levels in patients with HAE, and additional work is needed to fully understand these mechanisms.

MEASUREMENT OF C1-INH IN PLASMA

Diagnosis of HAE is confirmed using laboratory testing of the complement pathway, including C4 antigen, C1-INH antigen, and C1-INH function. Almost all untreated patients with HAE have low C4 levels. However, measurement of C1-INH antigen and C1-INH function levels is needed to confirm the diagnosis.³⁴ A C1-INH antigen test result can be used to identify patients with C1-INH deficiency, but measurement of C1-INH function is requisite to identify patients who have C1-INH protein that is present but dysfunctional.

Two methods are available for measuring C1-INH function in patients. The ELISA method detects protein complexes that form from the binding of C1-INH to activated C1s and is commercially available in the United States. The chromogenic method directly measures the inhibition of C1s and is currently only conducted at specialist laboratories in the United States.³⁵ Studies have shown that the chromogenic method is more reliable and provides less ambiguous results than the ELISA method.^{23,36} However, both assays measure C1-INH functional activity in the complement pathway, which may not be related to functional activity in the contact system, the primary pathway for bradykinin formation.²² An assay has been developed that directly measures C1-INH inhibition of factor XIIa and kallikrein,³⁷ which is more relevant to the pathogenesis of HAE. However, the assay is not yet commercially available.

THE RELATIONSHIP BETWEEN FUNCTIONAL C1-INH AND ANGIOEDEMA ATTACKS—EARLY OBSERVATIONS

The association between C1-INH functional activity and angioedema attacks was first described in 1984 by Spath et al.¹² In this study, the investigators measured C1-INH antigen and function levels in 111 plasma samples from 21 patients with HAE type 1. Most samples were collected while patients were receiving androgens, but some patients were receiving tranexamic acid and others were not receiving prophylaxis therapy. No attacks were observed in patients with C1-INH antigen concentrations above 0.075 g/L, which was approximately 40% of the normal value of 0.196 g/L.¹² Attacks were most frequent when C1-INH antigen concentrations were below 18% of normal (0.035 g/dL).

Subsequent reports found an association between functional C1-INH levels and disease severity. In a retrospective study of patients from Hungary and Romania,³⁸ untreated patients with more severe disease in the previous year had significantly lower functional C1-INH levels than those with mild disease or who were asymptomatic. In a subsequent study of Hungarian patients by the same group,³⁹ disease severity was followed prospectively

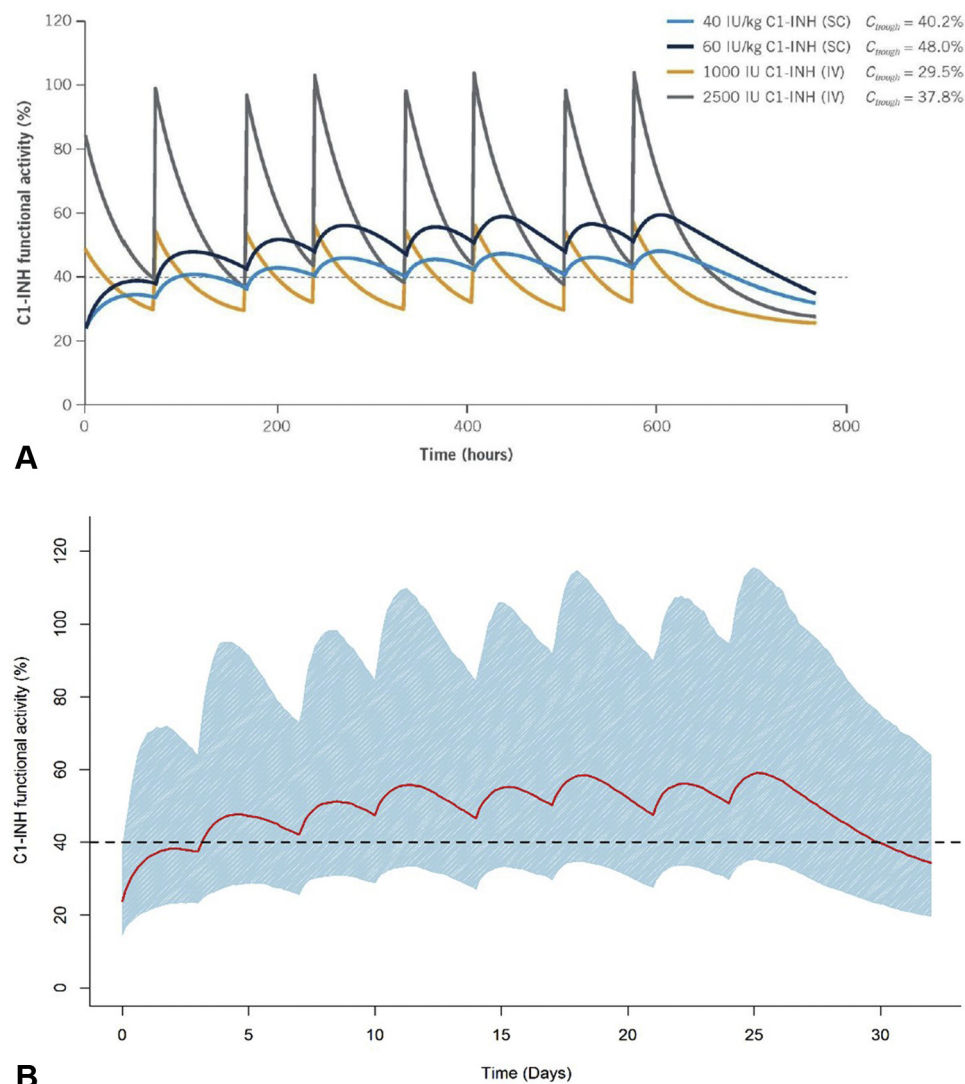


FIGURE 3. Pharmacokinetic models of C1-INH functional activity during prophylaxis treatment with plasma-derived C1-INH. **(A)** Median steady-state functional C1-INH activity during twice-weekly doses of 1000 or 2500 IU administered intravenously (IV) or 40 or 60 IU/kg administered subcutaneously (SC). Values for overall median trough functional C1-INH concentrations are shown in the key. **(B)** Simulated median (shaded region is 90% CI) functional C1-INH activity for twice-weekly doses of 60 IU/kg administered subcutaneously. Reprinted with permission from Pawaskar et al.⁴¹

after the measurement of functional C1-INH activity. Baseline functional C1-INH levels significantly negatively correlated with the number of attacks and the number of doses of C1-INH on-demand treatment. This result was observed in patients regardless of whether they were receiving prophylaxis therapy with androgens. The results of these studies provided preliminary evidence that low functional C1-INH increases the risk of an angioedema attack.

Others have suggested that C1-INH levels should be higher than 40% for adequate control. In studies of recombinant C1-INH in patients with HAE, Hack et al⁴⁰ found that functional C1-INH levels were more than 38% during 3 of 277 angioedema attacks (1% of all attacks evaluated). The highest functional C1-INH level was 46%. Measurements were taken after the attack started, so functional C1-INH levels may have been higher at the beginning of the attack. Because some attacks

occurred in patients who had functional C1-INH levels above the therapeutic threshold, the authors concluded that 40% is probably too low and that the goal of therapy should be to normalize C1-INH function levels to more than 70%, particularly when using C1-INH replacement therapy for the on-demand treatment of acute attacks. However, this study was not designed to evaluate the validity of the therapeutic target for prophylaxis treatment, which would require the measurement of functional C1-INH levels between attacks.

PROPHYLAXIS THERAPY WITH PLASMA-DERIVED C1-INH ADMINISTERED INTRAVENOUSLY

When intravenous plasma-derived C1-INH was first approved in the United States for prophylaxis therapy in 2008,⁷ the initially approved dosage was 1000 U administered intravenously every 3 or

TABLE I. Characteristics and pharmacokinetic parameters for subcutaneous C1-INH (human) HAEGARDA 60 IU/kg⁸

Description	Human plasma–derived, purified, pasteurized, lyophilized C1-INH concentrate
Indication (United States only)	Routine prophylaxis to prevent HAE attacks in adolescent and adult patients
Route of administration	Subcutaneous
Mechanism of action	C1-INH is a serine protease inhibitor that prevents the activation of factor XII, the conversion of prekallikrein to kallikrein, and the cleaving of bradykinin from high-molecular-weight kininogen. C1-INH is also involved in the complement, fibrinolytic, and coagulation systems
Clearance (CL), mean (95% CI)	1.03 (0.90-1.17) mL/h/kg
Volume of distribution (V_d), mean (95% CI)	0.05 (0.04-0.06) L/kg
Bioavailability, mean (95% CI)	42.7% (35.2%-50.2%)
Maximum C1-INH concentration (C_{max}), geometric mean (2.5-97.5 percentile of the population)	60.7% (31.8%-128%)
Trough C1-INH concentration (C_{trough}), geometric mean (2.5-97.5 percentile of the population)	48.0% (25.1%-102%)
Time to maximum C1-INH concentration (T_{max}), median (2.5-97.5 percentile of the population)	59 (23-134) h
Half-life, median (2.5-97.5 percentile of the population)	69 (24-251) h

4 days. After a single intravenous dose of 1000 U, the mean maximum C1-INH functional activity level was 67%, and the mean half-life was 56 hours.⁷ Pharmacokinetic studies show that C1-INH functional activity sharply increases to maximum levels within hours after intravenous administration and then gradually decreases until the next dose, resulting in a saw-tooth pattern (Figure 3, A).^{14,41} After an intravenous dose of 1000 IU, the trough functional C1-INH level is approximately one-half the peak level. Therefore, although intravenous administration of C1-INH quickly increases functional C1-INH levels above the therapeutic target, patients receiving 1000 IU may experience trough levels below the target before the next scheduled dose.

This decrease in functional C1-INH levels may explain why some patients receiving intravenous C1-INH have breakthrough attacks. In the randomized, placebo-controlled cross-over study of intravenous C1-INH prophylaxis,⁴² patients had a mean of 6.26 breakthrough attacks during the 12-week treatment period. In a long-term observational study of German patients, Bork and Hardt⁴³ noted that patients receiving C1-INH prophylaxis therapy developed a pattern in which attacks were more likely on the day of the next expected dose, which would correspond to the trough of the pharmacokinetic curve. This pattern was also observed in a European patient registry of intravenous C1-INH prophylaxis therapy, in which 69.7% of breakthrough attacks occurred on the day of the next expected dose.⁴⁴

In each of these studies, most patients were receiving 500 or 1000 U every 2 to 4 days. The product label for intravenous C1-INH prophylaxis allows for dose escalation up to 2500 U every 3 or 4 days.^{7,45} At this dose, pharmacokinetic modeling shows that peak and trough values are higher than the respective values at the 1000-IU dose (Figure 3, A),⁴¹ but the steady-state concentrations still display a saw-tooth pattern, with trough C1-INH functional levels approximately one-third of the peak levels. This pattern was also observed in a smaller study of intravenous weight-based dosing (25 U/kg) using a different formulation of plasma-derived C1-INH.⁴⁶

PROPHYLAXIS THERAPY WITH PLASMA-DERIVED C1-INH ADMINISTERED SUBCUTANEOUSLY

When C1-INH is administered subcutaneously, the steady state of functional C1-INH activity is more consistent compared with that of the intravenously administered C1-INH, and the difference

between peak and trough levels is smaller (Figure 3, A).^{14,41} After subcutaneous administration, C1-INH is slowly absorbed into the plasma, with a median time to maximum functional C1-INH activity of 59 hours, and trough levels that are approximately four-fifths the peak levels (Table I). Generally, subcutaneously administered drugs are expected to travel into the lymphatic system from the interstitial space and then absorb into the vascular system (Figure 4).⁴⁷ Pharmacokinetic modeling showed that at the Food and Drug Administration–approved dosage of 60 IU/kg twice weekly, median trough and peak functional C1-INH levels were consistently above the 40% therapeutic target (Figure 3, B).⁴¹ At the lower subcutaneous dose of 40 IU/kg, functional C1-INH levels were also more consistent than the intravenous dose, but at a lower level than the 60 IU/kg dose (Figure 3, A).

The pharmacokinetic profile of subcutaneous C1-INH prophylaxis and the resulting trough plasma functional C1-INH concentrations have implications for the efficacy of breakthrough attack prevention. In a phase 3, randomized, double-blind, cross-over study (COMPACT),¹³ patients receiving subcutaneous injections of C1-INH 60 IU/kg twice weekly for 16 weeks had a median 95% reduction in attacks compared with placebo. A population-based pharmacokinetic and exposure-response model of the data from this study showed a significant relationship between predicted functional C1-INH levels at the time of an angioedema attack and the relative risk of having an attack (Figure 5). The lower the functional C1-INH levels, the higher the relative risk of the patient having an attack compared with no treatment. Patients with normal functional C1-INH levels (~70% or greater) had a very low relative risk of an angioedema attack (<10%). The relative risk increased approximately linearly from 10% to 20% as functional C1-INH levels decreased from 70% to 40%. The risk of an attack increased exponentially from 20% to 100% as the functional C1-INH levels decreased from 40% to 20%. According to the model, functional C1-INH levels of 33.1%, 40.3%, and 63.1% corresponded to 50%, 70%, and 90% reductions in relative risk of an attack, respectively.⁴⁸ Mean observed functional C1-INH levels for patients receiving the 60-IU/kg dose in the COMPACT study were above 60% at each time point throughout the treatment period, whereas mean levels for patients receiving the 40-IU/kg dose did not reach 50% at any time point.^{13,41}

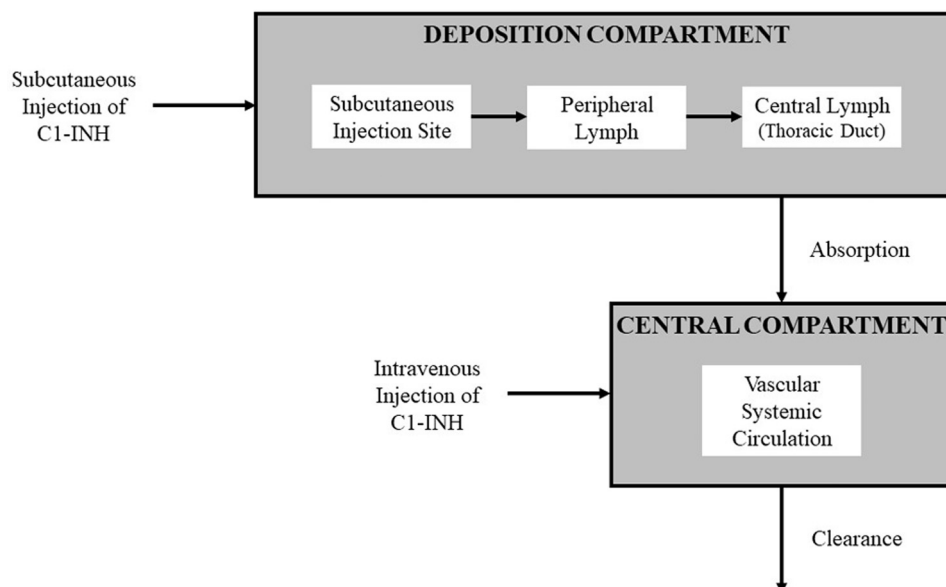


FIGURE 4. General model of absorption and clearance of subcutaneously and intravenously administered C1-INH. (Reprinted with permission modified from McLennan et al⁴⁷).

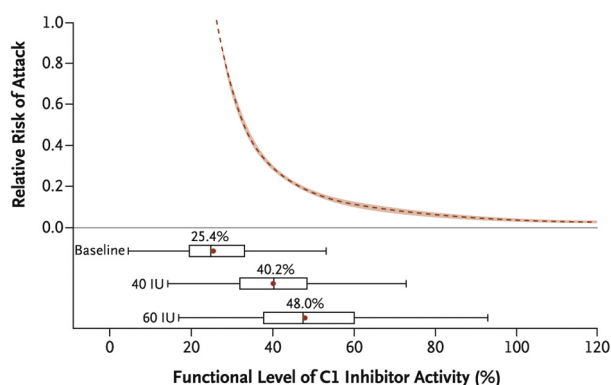


FIGURE 5. Population model of functional C1-INH levels and the relative risk of an angioedema attack. The red dashed line is the median of the model risk relationship, and the shaded area is the standard error. The box plots are the range of observed baseline and predicted trough steady-state functional C1-INH levels at doses of 40 and 60 IU/kg of subcutaneous C1-INH. In the box plots, the red dot is the geometric mean, the vertical line is the median, the box is the interquartile range, and the error bars are the minimum and maximum values. Reprinted with permission from Longhurst et al.¹³

Prophylaxis Therapy with Lanadelumab

Prophylaxis treatment with an mAb that inhibits active plasma kallikrein, lanadelumab, has been shown to be effective at reducing the frequency and severity of attacks in patients with HAE.⁴⁹ Theoretically, plasma kallikrein inhibition might prevent overconsumption of C1-INH, resulting in increases in C4. However, recently presented results from the phase 3 HELP study indicate that long-term treatment with lanadelumab did not affect functional C1-INH or C4 levels.⁵⁰ Although lanadelumab functions to inhibit plasma kallikrein as it forms during an

attack of swelling, it is essentially without function when the patient is well. Therefore, the patient continuously maintains low functional C1-INH levels.

DISCUSSION

The results of pharmacokinetic studies of patients with HAE who are receiving prophylaxis C1-INH therapy have shown that plasma functional C1-INH levels are closely related to the risk of having an angioedema attack.^{13,48} These results expand upon previous work that identified a threshold of approximately 40% of normal C1-INH antigen concentration above which was protective against an attack, whereas levels below approximately 20% indicated an attack was highly likely.¹² The pharmacokinetic studies show that the 40% threshold is near the inflection point of the continuous curve that models the relationship between functional C1-INH and the relative risk of an attack. As functional C1-INH levels decrease below this inflection point, the relative risk of an attack rapidly increases. Below the inflection point, the risk decreases asymptotically toward 0.

In vitro analysis of prekallikrein activation in the presence of increasing concentrations of C1-INH⁵¹ support the clinical results. In the absence of C1-INH or after addition of low concentrations, the prekallikrein-high-molecular-weight kininogen complex spontaneously activates even without a trigger. This activation is incrementally delayed with the addition of increasing concentrations of C1-INH and is not evident when C1-INH levels are at 70% of normal or above.

These *in vitro* and pharmacokinetic results help explain the clinical efficacy of subcutaneous C1-INH prophylaxis therapy. Subcutaneous administration of 60 IU/kg twice weekly in the COMPACT trial provided consistently high steady-state functional C1-INH levels, with mean values above 60% throughout the treatment period.¹³ Twice-weekly subcutaneous administration provides a more consistent steady state, with less difference between peak and trough values compared with intravenous

administration.^{14,41} Consistent maintenance of high levels of functional C1-INH reduced the risk of an angioedema attack. The lower dose of 40 IU/kg also produced a consistent steady state, but functional C1-INH levels were lower than those of the 60-IU/kg group (Figure 3). Although the COMPACT study was not designed to statistically compare the efficacy of individual doses, patients in the 40-IU/kg group had a numerically higher monthly attack rate and within-patient difference from placebo in monthly attack rate.¹³

These findings may also explain why some patients who receive intravenous prophylaxis C1-INH therapy require escalated doses⁴⁵ or reduced dose intervals, and why the frequency of attacks appear to be increased on the day of the next expected intravenous dose.^{43,44} Because of the saw-tooth pattern in the pharmacokinetic curve (Figure 3, A), patients receiving intravenous C1-INH prophylaxis therapy have low trough functional C1-INH levels, increasing the risk of an angioedema attack. Escalating the dose of intravenous C1-INH, or reducing the dose interval, raises trough functional C1-INH levels.

Importantly, these population-based pharmacokinetic and exposure-response models depict the relationship between functional C1-INH levels and the relative risk of an attack for the HAE population overall. Absorption and clearance rates of C1-INH and the response to treatment for individual patients are variable. This variability is depicted in the models of predicted functional C1-INH activity after treatment (Figure 5) and the actual observed functional C1-INH levels during the treatment period.¹³ Clearance rates of C1-INH are affected by various factors, including disease severity, time since the most recent attack, age, weight, and glycosylation of the C1-INH molecule. C1-INH is a heavily glycosylated protein, and glycosylation patterns affect the rate of clearance in the liver. Recombinant C1-INH has different glycosylation patterns than human plasma-derived C1-INH, which results in a lower half-life (3 hours).⁵²

However, although individual patients may have variable baseline functional C1-INH levels and clearance rates, the results of the COMPACT study show that the relative risk of an angioedema attack is closely related to functional C1-INH levels in patients receiving C1-INH for long-term prophylaxis. Now that this relationship has been confirmed, future studies can prospectively evaluate treatment protocols designed to optimize the dose for individual patients using C1-INH functional activity as a biomarker.

Individual patients with HAE with normal or nearly normal functional C1-INH levels may have a small but nonzero relative risk of an attack. The reasons for this are unknown, but several explanations are possible. First, measurement of C1-INH function in the plasma may not directly correspond to C1-INH function in the tissues where the attack occurs. Activation of the kinin-forming pathway along the surface of endothelial cells might occur when locally bound C1-INH is depleted faster than it can be replaced by C1-INH molecules from the plasma. In addition, factors that promote vascular permeability may inhibit C1-INH activity,⁵³ which could prevent C1-INH activity in a tissue region that is locally undergoing contact activation.

Second, the assays used to measure C1-INH function do not evaluate the functional ability of C1-INH in the kinin-forming pathway, which is the primary cause of angioedema attacks. The chromogenic and ELISAs measure the ability of C1-INH to inhibit C1s in the complement pathway, which is not directly

involved in the production of bradykinin. Assays that directly measure C1-INH inhibition of factor XIIa and kallikrein have been developed,³⁷ but are not yet commercially available. Of note, during the validation of these assays, all patients with HAE had functional C1-INH levels below 40% according to the assays that measured inhibition of factor XIIa and kallikrein, while some patients had functional activity above 40% according to the method that measured complement inhibition.³⁷ This result suggests that some patients may produce C1-INH proteins that are less functional in the contact pathway than the complement pathway. A recent study of 10 patients who had been diagnosed with idiopathic nonhistaminergic angioedema and had normal C4 levels and normal functional C1-INH levels according to the standard chromogenic assay that measures C1s inhibition found that 4 of the patients had low functional C1-INH levels according to assays that measure factor XIIa or plasma kallikrein inhibition.⁵⁴

The pharmacokinetic studies of subcutaneous C1-INH were the first to prospectively evaluate the relationship between a biomarker and the risk of an attack in patients with HAE. Previous studies have evaluated the association between other biomarkers and disease activity, including cleaved high-molecular-weight kininogen⁵⁵ and vascular permeability factors^{56,57} (reviewed by Kaplan and Maas⁵¹). These studies show that the levels of such biomarkers are increased in patients with frequent attacks versus infrequent attacks or during an attack compared with an asymptomatic period. However, none have specifically evaluated the association between biomarker levels and the risk of an attack over time. Given the relationship between functional C1-INH levels and angioedema attack risk in patients with HAE who are receiving C1-INH prophylaxis therapy, measurement of functional C1-INH levels may inform clinical decision making, particularly if a patient experiences a decrease in response.

CONCLUSIONS

Functional C1-INH has been used as a diagnostic tool to identify patients with C1-INH deficiency for decades. The results of recent studies confirm that functional C1-INH may also be used as a biomarker that is associated with the risk of an attack in patients with HAE who are receiving long-term prophylaxis with C1-INH replacement therapy. This information may be useful for decisions about treatment and dosage. Future studies should evaluate the utility of functional C1-INH measurement to guide decision making in usual clinical practice.

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