
Hereditary angioedema: a current state-of-the-art review, VI: novel therapies for hereditary angioedema

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Objective: To provide a comprehensive overview on clinical trial design and results of emerging therapies for the treatment of hereditary angioedema (HAE).

Data Sources: MEDLINE or PubMed literature searches were conducted to identify double-blind, placebo-controlled trials investigating C1 esterase replacement, kallikrein inhibitor, and bradykinin receptor 2 antagonist therapies.

Study Selection: Ongoing trials or those just recently completed from all companies developing a product for the treatment of HAE are discussed.

Results: All of these agents are believed to be effective when tested in patients in phase 1 or phase 2 trials. The studies have many features in common, including being placebo-controlled and blinded; having a preliminary screening visit at which the diagnosis is confirmed; having either low circulating C1 inhibitor protein levels or low levels of functional C1 inhibitor, low C4 levels, and normal C1q levels; enrolling individuals who are relatively early in attacks (4–6 hours from the onset); and stipulating that patients continue taking the medications that they have been taking in the long term. The type of attack acceptable for each treatment protocol varies from study to study. Some allow peripheral edema attacks, some facial attacks, and in some studies, the Food and Drug Administration has allowed purified serum C1 inhibitor to be used as a rescue medication if the patient remains in difficulty after the study drug has been used and found to be ineffective.

Conclusion: The outlook for new, effective short-term therapy appears to be excellent. In the near future, a whole new therapeutic armamentarium to care for patients with HAE should be available in the United States.

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INTRODUCTION

This study was conducted to provide a comprehensive overview on clinical trial design and results of emerging therapies for the treatment of hereditary angioedema (HAE). We performed MEDLINE or PubMed literature searches to identify double-blind, placebo-controlled trials investigating C1 esterase replacement, kallikrein inhibitor, and bradykinin receptor 2 antagonist therapies. Ongoing trials or those just recently completed from all companies developing a product for the treatment of HAE are discussed.

Currently, 5 companies are attempting to make available therapy for acute attacks of HAE. Two of these companies, Lev Pharmaceutical (New York, New York) and CSL Behring (King of Prussia, Pennsylvania), are introducing purified C1 inhibitor protein prepared from pooled plasma of thousands of donors. C1 inhibitor is the protein that is partially deficient in these patients; therefore, the goal of this therapy is to replace the missing plasma protein. One company, Pharming (Leiden, The Netherlands), is introducing a recombinant C1 inhibitor protein preparation. Dyax (Cambridge, Massachusetts) is introducing a kal-

likrein inhibitor, DX88. Since the plasma enzyme kallikrein, acting on the substrate high-molecular-weight kininogen, releases bradykinin, kallikrein inhibition prevents bradykinin generation and, therefore, should prevent attacks of HAE. Finally, a fifth company, Jerini (Berlin, Germany), is developing a bradykinin type 2 receptor antagonist, Icatibant. Icatibant will block the bradykinin type 2 receptor, thought to be responsible for initiating the plasma leakage associated with the angioedema attack, to prevent attacks. All the companies are enthusiastic about their product. Trials are ongoing or have just recently been completed for all of these companies, and all of these agents have been believed to be effective when tested in patients in phase 1 or phase 2 trials.

The studies have many features in common. All are placebo-controlled, blinded trials, with each subject receiving either drug or placebo once. All have a preliminary screening visit at which the diagnosis is confirmed. Patients are to have either low circulating C1 inhibitor protein levels, true of 85% of patients, or low levels of functional C1 inhibitor, low C4 levels, and normal C1q levels.¹ The requirement for normal levels of C1q is in place to rule out entry of patients with acquired C1 inhibitor deficiency.² All these studies enroll individuals who are relatively early in attacks. In the various studies, patients must enter the study 4 to 6 hours from the start of an attack because none of the companies want to enter patients whose attacks may resolve spontaneously. If such were the case, it would confound the study by suggesting efficacy of placebo. All studies stipulate that

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patients continue taking the medications that they have been taking in the long term. The dose of androgen is not changed once an attack starts. Most suggest that narcotic treatment for abdominal pain is not acceptable or is deemed a treatment failure. The type of attack acceptable for each treatment protocol varies from study to study. Some allow peripheral edema attacks to be included for the protocol, some do not. Some allow facial attacks, some do not. For some studies, the Food and Drug Administration (FDA) has allowed purified serum C1 inhibitor to be used as a rescue medication if the patient remains in difficulty after the study drug has been used and found to be ineffective. In others, the rescue medication is the drug under investigation used in an unblinded fashion.

Evolution of C1 Esterase Inhibitor Replacement Therapies

In 1963, Donaldson and Evans³ described a deficiency of C1 inhibitor in patients with HAE, and by the 1970s, multiple

organizations that had ongoing purification procedures for the isolation of IgG from plasma turned their attention to isolating C1 inhibitor protein. In particular, the Dutch Red Cross, Behring Pharmaceuticals in Germany, and the American Red Cross set out to make pilot runs of purified C1 inhibitor. In 1974 in the United States, the American Red Cross began to make experimental batches of C1 inhibitor from plasma in their small-scale research facility. Gadek et al⁴ reported the biochemical effect of the Red Cross preparation in 8 patients with HAE and noted the effectiveness of the preparation in the treatment of HAE attacks in 5 patients. One patient was treated successfully on 3 separate occasions. Years later, it was discovered that one of the asymptomatic patients did not have HAE but had acquired angioedema with monoclonal anti-C1 inhibitor. It is interesting that this patient was the only one who did not have a significant biochemical response to the infusion. With the onset of the AIDS

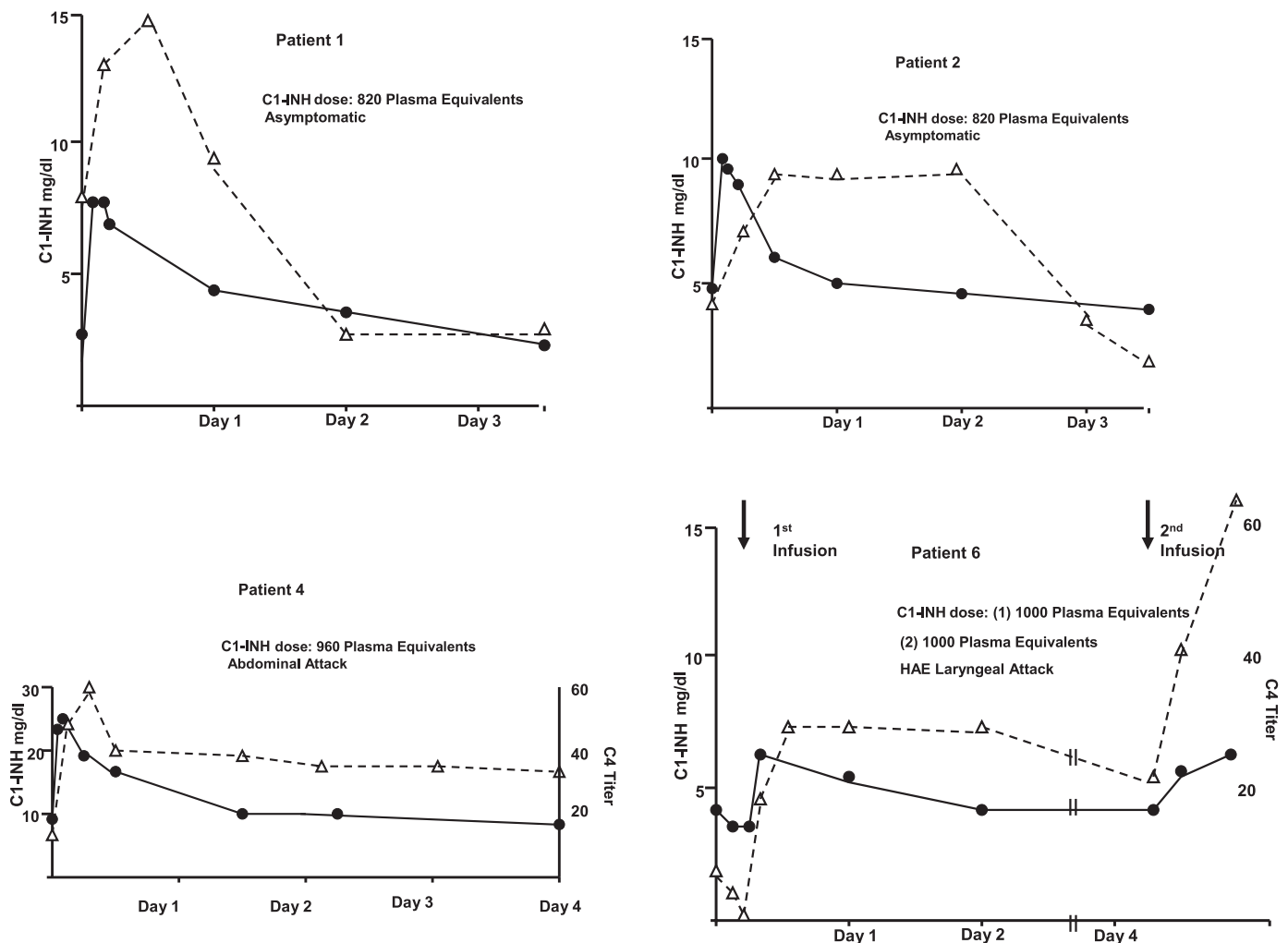


Figure 1. C1 inhibitor (C1-INH) infusion in patients with asymptomatic and symptomatic hereditary angioedema (HAE). Reprinted with permission Gadek et al.⁴

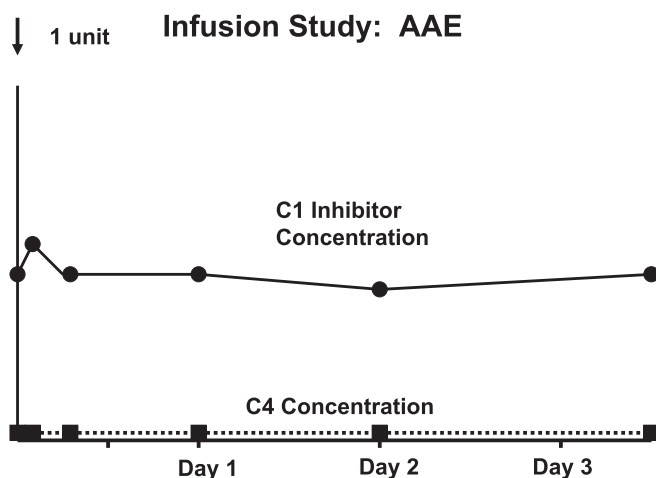


Figure 2. Infusion of C1 inhibitor into a patient with acquired C1 inhibitor deficiency. Filled circles indicate C1 inhibitor; filled squares, C4.

epidemic starting in the United States in 1980, preparation of this plasma protein by the American Red Cross was halted and the Red Cross never resumed preparing large batches.

Figure 1, reprinted from the *New England Journal of Medicine*, shows the effect of C1 inhibitor in 4 patients with HAE.⁴ Two of the patients were having HAE attacks at the time of the infusion. It is striking that these data obtained in the 1970s are similar to the data being generated now. On intravenous infusion, the plasma C1 inhibitor level increased rapidly, with the C4 level also rising but far later than the C1 inhibitor level. The elevated C4 level was sustained longer than that of C1 inhibitor. The blood level of the C1 inhibitor decreased rapidly, reflecting its short half-life. In 1 patient illustrated in Figure 1 and treated during an HAE laryngeal attack, a second infusion was given on day 4, with again a rapid increase in C1 inhibitor and a slower increase in C4. All of the patients with HAE having attacks responded to therapy. The lack of biochemical response to therapy in a patient with acquired C1 inhibitor deficiency, an HAE-like syndrome due to the presence of monoclonal anti-C1 inhibitor antibody, who was not having an attack is shown in Figure 2. In this patient, the presence of the monoclonal antibody led to rapid inactivation and loss of the infused C1 inhibitor.

Table 1. Virus Reduction During Purification^a

Step	LE virus			NLE virus	
	BVDV	HIV	PRV	CPV	HAV
Polyethylene glycol precipitation	>4.5	>5.1	>6.0	>5.4	>2.8
Pasteurization	>6.7	>6.1	>6.7	0.1	>2.8
Nanofiltration	>5.5	>5.6	>6.4	>4.5	>4.9
Total	>16.7	>16.8	>19.1	>10.0	>10.5

Abbreviations: BVDV, bovine diarrheal virus; CPV, canine parvovirus; HAV, hepatitis A virus; HIV, human immunodeficiency virus; LE, lipid envelop; NLE, nonlipid envelop; PRV, pseudorabies virus.

^a Data are from Lev Pharma.

Here, there was no increase in C4 level, and the level of C1 inhibitor present in the patient showed only a small increase just after the beginning of infusion of therapy.

At approximately this same time, the Dutch Red Cross became interested in purifying plasma C1 inhibitor. It is that preparation that is currently being studied in the United States by Lev Pharmaceuticals. Their first batches of C1 inhibitor were prepared from plasma as early as 1972. Anagastoni et al⁵ reported that the preparation was effective in the treatment of HAE in a case report in 1978 and in a longer report in 1980. They did not provide detailed biochemical or clinical data with these reports. The plasma protein manufacturing arm of the Dutch Red Cross merged into Sanquin in 2003, and, over the years, the manufacturing techniques used by all companies have been improved. For example, all companies treat plasma protein preparations with detergents designed to destroy the membranes of enveloped viruses. In 1989, heat treatment was added to plasma preparation to further reduce the possibility of viral contamination, and, more recently, a nanofiltration step has been added by Sanquin. These various steps are added to attempt to develop a preparation that has little danger of contaminating viruses, either enveloped or not enveloped. Table 1, which was supplied by Lev Pharmaceuticals, shows the effect of nanofiltration and the other steps in purification on a plasma preparation that is purposely contaminated with a series of lipid-enveloped viruses or non-lipid-enveloped viruses such as canine parvovirus or hepatitis A. Many logs of purification are achieved. All companies that deal with donated plasma go through relatively similar procedures to prove the efficacy of purification procedures.

CSL Behring in Germany also began to prepare C1 inhibitor in the 1970s. It was first licensed as a nonpasteurized product in Germany in 1979 and as a pasteurized product in 1985. It has been approved either as a licensed product or for compassionate use in many countries since the early 1980s. It has been reported on extensively by Bork and colleagues.⁶ Bork⁷ first mentioned the use of C1 inhibitor to terminate an attack in a case report in 1979, although no biochemical data were given at that time.

The Lev Pharmaceuticals product has been in clinical trials, and, recently, it was announced that these clinical trials have shown a statistically significant treatment difference between drug and placebo. The CSL Behring product has just completed clinical trials and also announced highly statistically significant results. Both of these preparations have been in use in Europe for well more than 20 years and both are highly purified proteins. I am told by both companies that neither has been associated with the transmission of infectious agents. As mentioned, the Lev Pharmaceuticals product is manufactured in the Netherlands. The CSL preparation is manufactured in Germany, but both use plasma collected in the United States and are extensively tested for viruses as required by the FDA.

The clinical signs of HAE can be markedly influenced by psychological factors, and double-blind study of the use of these agents was of great importance. The first double-blind study of C1 inhibitor purified from plasma was conducted by Waytes et al and reported in 1996.⁸ The product tested was a vapor-heated C1 inhibitor prepared from plasma by Immuno Pharmaceuticals,

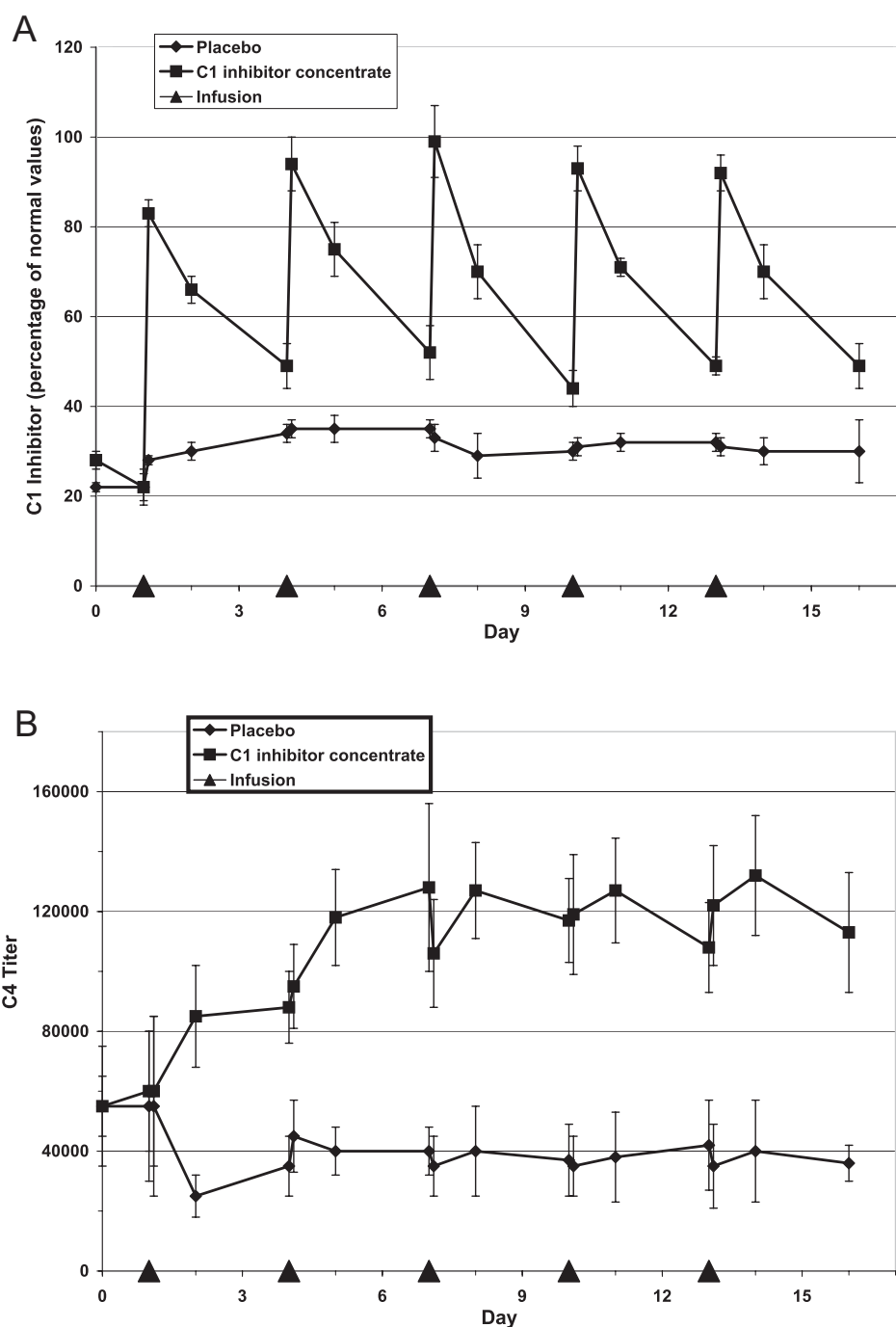


Figure 3. Infusion of C1 inhibitor into a patient with hereditary C1 inhibitor deficiency. Filled circles indicate C1 inhibitor; filled squares, C4.

Austria, a product also available in Europe. It was impure in terms of percentage of C1 inhibitor per total protein but was biologically effective. The study was performed in 2 locations. The inpatient study was performed by my group with Dr Thomas Waytes at the National Institutes of Health. In this study, patients with severe disease were hospitalized, random-

ized, and given C1 inhibitor or placebo intravenously every 3 days. Their clinical symptoms were evaluated, and blood was taken for C4 and C1 inhibitor levels. The outpatient portion of the study was performed at Boston Children's Hospital by Dr Fred S. Rosen and colleagues. In the study by Rosen et al, patients having angioedema attacks were administered C1 in-

Table 2. Length of Time to Response With C1 Inhibitor or Placebo^a

Location of edema	Response in <30 min		Response in <240 min	
	C1 inhibitor	Placebo	C1 inhibitor	Placebo
Abdomen	25/35 (71)	0/34	35/35 (100)	2/34 (6)
Larynx	3/4 (75)	0/4	4/4 (100)	1/4 (25)
Face	7/7 (100)	0/8	7/7 (100)	1/8 (12)
Extremities	9/16 (56)	1/16 (6)	13/16 (81)	3/16 (19)
First 3 locations	33/44 (75)	0/40	44/44 (100)	4/40 (10)
All locations	38/55 (69)	1/49 (2)	52/55 (95)	6/49 (12)

^a Data are number (percentage) of patients.

hitor or placebo and evaluated in an outpatient setting. Patients were asked to estimate if and when their clinical symptoms began to resolve. Some of our reported findings were used in the development of a Baxter trial that used the same C1 inhibition preparations some years later.

Figure 3 shows the results of the inpatient portion of the C1 inhibitor study. As seen in Figure 3A, infusion of C1 inhibitor led to a rapid rise in blood C1 inhibitor levels and a rapid decrease thereafter, giving blood levels a sawtooth pattern. Infusion of placebo essentially did not change the C1 inhibitor level. As in the earlier study (Figure 3B), the C4 level gradually increased in patients treated with C1 inhibitor to the point where, at approximately 3 days, the level was above the lower limit of normal for C4. Again, in placebo-treated patients, the level did not change. In the outpatient portion of the study, patients were asked to evaluate attacks and determine or estimate when they thought their attacks were improving (Table 2). As noted, essentially all of the patients thought they were improving by 4 hours, the only exception being a few patients whose attacks were associated with angioedema of the extremities. In this case, it appears that the absorption of the edema fluid from peripheral sites is slower than absorption from the gastrointestinal mucosa. Many of the patients thought that their attacks were starting to

resolve at 30 minutes, which was not true of the patients in the placebo-controlled arm. Overall, we interpreted this double-blind study to indicate that C1 inhibitor was effective in terminating attacks of HAE. Unfortunately, these data were not used by Immuno Pharmaceuticals as the basis for a submission to the FDA. Immuno Pharmaceuticals was purchased by Baxter; another trial was performed in which much reliance was placed on the outpatient study end point, which suggested that attacks began to show improvement within 30 minutes to an hour. The Baxter trial relied on that end point and was a failure. It is the failure of the Baxter trial that has led in part to the tremendous interest in these new agents at the present time.

In 2005, Bork et al⁹ reported estimates of the time to relief of abdominal pain in a large group of patients treated with the plasma purified C1 inhibitor prepared by CSL Behring, Berinert. As noted, Bork directs a center that collects data from many patients from all over Germany and enormous numbers of patients were treated. Many of the patients started to find relief of symptoms within 30 minutes. The data in this report do not come from a blinded study, and some of the patients were queried afterward about their time to relief. Nevertheless, Bork et al found that in all patients and in the patients with the most severe conditions, the duration of attacks, the amount of vom-

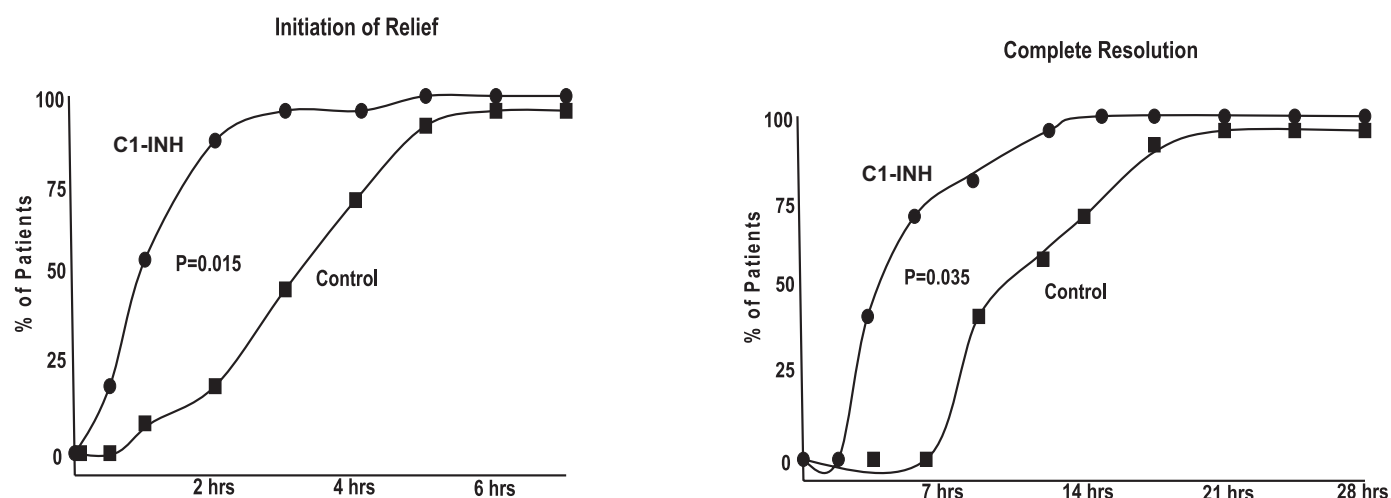


Figure 4. Effect of self-administration of C1 inhibitor (C1-INH) on initiation of relief and complete clearing of abdominal pain. Controls are recollection of the rate of relief. Reprinted with permission from Levi et al.¹⁰

iting, the level of pain, and the amount of diarrhea were much improved in the patients given purified C1 inhibitor. Levi et al,¹⁰ studying the Lev Pharmaceuticals preparations, have reported on the use of self-administered C1 inhibitor. As shown in Figure 4, reprinted from the *Journal of Allergy and Clinical Immunology*, self-administration at home of C1 inhibitor caused a rapid initiation of symptom relief and early complete resolution of attacks. It must be mentioned that the control group in this study was not patients given placebo at the time of attack but recollection by patients of their previous attacks; therefore, the control numbers may not be entirely accurate. Levi et al and later Longhurst et al¹¹ also reported that self-administration of C1 inhibitor on a regular basis could decrease attack frequencies, in some cases, to zero and that C1 inhibitor only had to be infused once a week. This finding is important because one of the major problems that patients have is the problem of traveling to a hospital emergency department for treatment and often a stay in the emergency department, which may extend for many hours. The dose of C1 inhibitor that has been used to terminate attacks has been in the range of approximately 20 to 25 U/kg, with 1 U representing the amount of activity in 1 mL of plasma.

RECOMBINANT C1 ESTERASE INHIBITOR REPLACEMENT THERAPY

The third product under development is prepared by the Dutch Company Pharming. For this product, the human gene for C1 inhibitor has been introduced into animals, in this case rabbits, under the gene regulatory control of a bovine α S1-casein promoter.¹² Under these conditions, the human protein is secreted in the milk of the rabbit and the milk can be collected and the human protein isolated. Thus far, we have relatively little information about this material, but details of the pharmacokinetics have been reported. It has been reported that patients respond to therapy with this material. Because the rabbit-produced C1 inhibitor is glycosylated differently than the normal human protein, it has a much shorter half-life; in the recipient, the half-life is dose related. The half-life at 100 U/kg is only approximately 3 hours. Use of the product has been shown to lead to the rapid disappearance of C4 fragments from patient's serum. Since the effect of C1 inhibitor is to prevent the cleavage of C4 and C2 by activated C1, and since this cleavage continues in the absence of C1 inhibitor, the presence of C4 fragments in the circulation is an indication of uncontrolled activation of C1, and the disappearance of these fragments suggests that the infused C1 inhibitor was effective in inhibiting C1. Pharming states that the product reliably terminates attacks as noted in phase 1 and phase 2 studies and has just completed a phase 3 double-blind trial.

DX88: A KALLIKREIN INHIBITOR

The fourth product in development is DX88, manufactured by Dyax. DX88 is a reversible inhibitor of the enzyme plasma kallikrein.^{13,14} It is a 60-amino acid peptide derived from a Kunitz domain structural backbone with 7 unique amino acids. The kallikrein on rate of this inhibitor (binding to enzyme) is $2 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ and the off rate is $2 \times 10^5 \text{ s}^{-1}$. Thus, it binds rapidly and is released more slowly. This material can be ad-

ministered intravenously or subcutaneously. It is usually kept frozen before administration. It is specific and has a high apparent inhibition constant (K_i) of 4×10^{11} . The C1 inhibitor has a K_i of only 1.7×10^4 for plasma kallikrein. DX88 does not strongly inhibit activated C1r or C1s, and these 2 subunits of C1, as active enzymes, are inhibited more strongly by C1 inhibitor. It has a relatively low affinity for coagulation factors XIIa and XIa. C1 inhibitor has a relatively low affinity for these products as well. When DX88 was given to mice in Dr Davis' mouse model of C1 inhibitor deficiency and the animals are challenged with mustard oil, the DX88 in a dose-dependent fashion decreased the extravasation of albumin with bound Evans blue into the tissues, suggesting prevention of bradykinin-induced angioedema.¹⁵

BRADYKININ RECEPTOR ANTAGONISTS

The final product is Icatibant. Icatibant is a bradykinin type 2 receptor antagonist. It is a potent, specific, reversible, competitive 10-amino acid peptide antagonist of this receptor with an inhibitory concentration at 50% of 1.4 nM.^{16,17} This receptor is a member of the 7-transmembrane spanning receptor superfamily. This peptide is not effective against the bradykinin type 1 receptor, which optimally recognizes des-Arg-bradykinin. Icatibant is 96% bioavailable after subcutaneous injection, and patients are being studied with abdominal cutaneous and laryngeal edema attacks. Two trials have been completed, a FAST-1 (For Angioedema Subcutaneous Treatment) trial and a FAST-2 trial. The FAST-1 trial in Europe studied drug against a control agent, tranexamic acid, which is not thought to be highly effective in acute attacks. The trial in the United States (FAST-2) studied drug against placebo. The trial in Europe showed a statistically significant difference between the drug and tranexamic acid, and the US trial missed statistical significance. The protocol developed by Jerini pooled data from multiple types of attacks, and it may be that pooling different kinds of attacks led to difficulty in adequate comparisons of numerical data. Like DX88 and purified C1 inhibitor, Icatibant prevents capillary leak in the Davis C1 inhibitor-deficient mouse model. Like the other agents, this agent is thought to be effective in patients.

CONCLUSIONS

At this point, relatively little has been published about any of these new clinical trials. Nevertheless, it is clear they all have theoretical problems and theoretical advantages. The plasma products are likely to be effective, since they represent replacement of the missing protein. This protein under physiologic conditions prevents attacks. Plasma protein infusion always carries the risk of infection. In this case, the risk is relatively minor, according to the manufacturers, since no infection has been observed with the current products, and they have been used for more than 20 years. Both start with the blood of healthy donors and go through potent virus reduction purification. The disadvantage of these products is that they are currently being given intravenously rather than subcutaneously as some of the other products are. Since all patients are heterozygotes and make normal protein, significant allergy to the administered product is unlikely.

In the case of recombinant C1 inhibitor, glycosylation differs from normal C1 inhibitor and the half-life of the product is short. Given the difference in glycosylation, there is some risk of hypersensitivity, and certainly there is some risk of allergy from contaminating rabbit protein, although the C1 inhibitor itself is highly purified. Two advantages of this product are that it is not prepared from pooled human plasma and therefore is unlikely to contain infectious human pathogens. Since it is made in animals, theoretically the supply is limitless.

The kallikrein inhibitor (DX88) and the bradykinin receptor antagonist (Icatibant) are both foreign peptides. In both cases, there is some risk of allergy with repeated administration and their half-life of action is short. We know little about the long-term effect of bradykinin inhibition in humans. Since these attacks in patients usually do not occur extremely frequently, and since it is not proposed to use these agents in the long term, this is probably not a long-term problem. Nevertheless, cardiac difficulties have been seen in animals with long-term administration of high-dose bradykinin receptor antagonists. As mentioned, both products are given subcutaneously, both are relatively inexpensive to make compared with the serum product, and there is no risk of infection.

Subcutaneous administration of interferon gamma has been recommended for therapy of HAE by multiple authors, since it induces C1 inhibitor synthesis by cells in vitro. When Dr Chiam Brickman was a fellow in our laboratory, we studied with him interferon gamma as an inducer of C1 inhibitor in patients with HAE. We administered interferon gamma to a group of patients with HAE at several dosage levels. The level of C1 inhibitor in all the patients increased, and it appeared that the patients' attack frequency may have slowed. Since this was not a double-blind study, attack frequency was estimated. We stopped the study because all of these patients experienced many toxic effects from the interferon injection, including fevers, muscle aches and pains, and distress. The interferon gamma in these studies was administered subcutaneously at doses of 25, 37, and 50 $\mu\text{g}/\text{m}^2$ in various patients. We believed at that time that interferon was not a useful therapy.

The outlook for new, effective short-term therapy appears to be excellent at this time. In the near future, we will have a whole new therapeutic armamentarium to care for patients with acute attacks. In addition, long-term therapy may be used much less frequently as it becomes possible to terminate attacks rapidly once they start.

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