

Update on Preventive Therapy (Prophylaxis) for Hereditary Angioedema

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KEYWORDS

• Hereditary angioedema • Prophylaxis • C1 inhibitor • Androgens • Antifibrinolytics

KEY POINTS

- The introduction of new and effective therapy to terminate acute attacks of angioedema in patients with hereditary angioedema has revolutionized the treatment landscape.
- Both attenuated androgens and inhibitors of fibrinolysis were found to provide effective preventive oral therapy in double blind studies, but each group causes unacceptable side effects or is inappropriate as therapy in some patients.
- In 2009, plasma derived C1 inhibitor was approved for prophylaxis in appropriate patients. The major disadvantage of this agent is that currently it must be administered by intravenous injection 2–3 times a week.
- Some patients require short term prophylaxis following trauma or prior to surgery. The drugs above have been used effectively in this setting and fresh frozen plasma has also proved to be useful prior to surgery.

INTRODUCTION

The introduction of new and effective therapy to terminate acute attacks of angioedema in patients with hereditary angioedema (HEA) has revolutionized the treatment landscape. In the past in America, prophylactic treatment to prevent the occurrence of attacks was the only reliable therapeutic option. Now there are multiple treatment modalities that have been proved to terminate attacks within hours and that have received Food and Drug Administration (FDA) approval. Nevertheless, there continues to be a need for long-term and short-term prophylaxis. Long-term prophylaxis is the designation given to long-term preventive therapy. Unlike the situation where each acute attack is treated, with effective prophylaxis attacks do not occur. Given the enormous morbidity of this disease, the high costs of the disease in terms of physician and hospital costs, and the costs of missed work and patient's being unable to work, prophylaxis to prevent attacks has always had high priority.¹ Short-term prophylaxis also

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has a place in therapy when patients are not having attacks, but are in danger of having an attack in the near future. Thus, a patient undergoing surgery, having extensive dental work, or in a traumatic accident might be treated to prevent a possible future attack. The need for such treatment is clear. Many patients have attacks precipitated by trauma. If the trauma of dental manipulation or gum injection leads to angioedema starting in the mouth, airway compromise may result. In the days before prophylaxis, these patients learned to dread going to the dentist. Short-term prophylaxis addresses this possibility. Although as discussed, acute and effective therapy is now available if such swelling was to occur, the advantages of a preventative approach are obvious.

DEVELOPMENT OF THE OLDER AGENTS

Long-term preventive therapy for HAE was addressed long before we had knowledge of disease pathogenesis. A Swedish group, interested in defining diseases in which a newly described drug epsilon-aminocaproic acid (EACA), a fibrinolysis inhibitor, might be useful, administered the drug to patients with a wide variety of diseases.² They reported their experience in treating many diseases over a 5-year period. It was noted that a single patient with HAE seemed to improve on EACA. The report was noted by another Swedish group who treated a second patient with EACA and confirmed the finding.³ This latter group was interested in the effect of EACA therapy on complement activation and histamine generation, the mediators thought at that time to be responsible for the angioedema. The group found no clear effect on either mediator pathway. They were unable to identify the mechanism by which EACA controlled the development of angioedema. A year later, Champion and Lachmann reported another family successfully treated with EACA.⁴ Frank and colleagues⁵ in 1972 conducted a double-blind study of the EACA prophylaxis, proving that EACA was far more effective than placebo in controlling attacks. In Europe, a cyclical derivative of EACA, tranexamic acid, was developed and has become the standard fibrinolysis inhibitor used in the treatment of HAE, because it is more convenient to use and has a better toxicity profile.⁶ Blohme and colleagues studied the usefulness of this agent in HAE treatment and published a double-blind study showing that it is quite effective in prophylaxis. Tranexamic acid was not available in capsule form in America until recently and has not been widely used in this country. EACA has been used in this country, particularly for treatment of children, and is associated with a wide variety of long-term toxicities. With long-term EACA therapy, thrombosis has not been a problem in this investigator's experience, although it certainly is a theoretical problem, particularly in older individuals, but muscle aches and pains with weakness and markedly elevated creatine phosphokinase enzymes and a feeling of severe fatigue to the point of disability are commonly noted. It is now thought that EACA functions in HAE prophylaxis by inhibiting plasmin activation of kallikrein and that by interrupting the kinin generating cycle, it tends to inhibit attacks, but this has not been studied carefully and it remains a supposition. Because use of EACA was clearly associated with great difficulty over time, more effective and safer prophylactic agents were needed.

Frank and colleagues⁷ were struck by the endocrinologic aspects of HAE. The disease, inherited as an autosomal dominant trait, is equal in incidence in men and women and becomes worse at the time of puberty in both sexes. Nevertheless, they noted that it is made much more severe by estrogens, such as those in birth control tablets and most patients who come to a clinic are women. In their experience, most women were much improved clinically during the latter part of pregnancy and many of the patients who they were observing said that the last trimester of pregnancy was the best period that they had experienced clinically in many years. They never had attacks

precipitated by the trauma of delivery, although some of the patients often had attacks precipitated by other trauma. These findings were not uniformly true and a minority of the women seen in Frank's clinic became much more severely ill during pregnancy. The observation is of interest because German investigators have reported that German women have no clear change in severity in pregnancy and the Australians have reported that their experience is similar to that in Frank's clinic.⁸ A recent European report based on a questionnaire sent to a large number of European women came to the conclusion that about one-third of patients got better, one-third became worse, and about one-third had no change.⁹ The reasons for these differences are unknown, but it is of interest that pregnant women in America were on no therapy, whereas women in Germany had available purified C1 inhibitor to rapidly terminate attacks.

Because progesterone rises progressively during pregnancy and falls precipitously on delivery, Frank's group first studied the effect of progesterone as prophylaxis in a small group of patients. The essentially negative study was never published. Although they noted that all of the treated women felt better and reported fewer symptoms, there was no decrease in the frequency of attacks when the drug was compared with placebo. Other more recent uncontrolled studies suggest that some women will respond well to this agent.

Our group set out to find a gonadotropin inhibitor that would decrease the synthesis of estrogens in men and women. The drug chosen for study was danazol, a gonadotropin inhibitor that was being developed as a contraceptive for women and that was felt to be safely used in women. In a double-blind study, it was shown that this drug is extremely effective in prophylaxis of HAE (**Table 1**) and in some patients, surprisingly, raised the blood level of C1 inhibitor to normal.¹⁰ The drug was so effective that it was approved by FDA for HAE prophylaxis on the basis of study of these 9 patients. Because patients are heterozygotes, they have one normal gene allele and one abnormal gene; the finding suggests that the functional output of the normal allele increases on danazol therapy. There are data to support and refute this suggestion and the question is not settled. Over the next years, it was quickly discovered that all of the 17-methylated and attenuated androgens are useful in the prophylaxis of HAE. Testosterone itself is not effective. A similar androgen, stanozolol, also received FDA approval for HAE therapy following a double-blind study, but it is currently only obtained in the United States through compounding pharmacies.¹¹ Interestingly, it also has been found that androgens increase the level of bradykinin degrading enzymes like aminopeptidase P.¹² At present it seems that androgens both decrease the formation of bradykinin by increasing C1 inhibitor levels and increase its degradation by degrading enzymes, thereby preventing these bradykinin-initiated attacks, but this is by no means settled.

Table 1

Results of a double-blind study of the use of danazol versus placebo in HAE prophylaxis. Patients received drug or placebo for about a month. At the end of each study period, they went on to the next random drug or placebo course. If the patient experienced an attack, the course that they were on was deemed a failure and they continued immediately to the next random course. The marked effect of danazol in prophylaxis is evident

	Danazol Treatment Results		
	Total Courses	Attack-Free Courses	Attacks
Placebo	46	3	43
Danazol	42	41	1
Total	88	44	44

Although the original FDA approval of danazol was based on the results in very few patients, the drug has come to be used around the world and there is now a great deal of clinical experience with its use. In an interesting study in 2008, Bork and Barnstedt¹³ reported a retrospective analysis of the Danish and German experience in treating 118 patients for an average of 11 years. The drug was effective in the vast majority of patients; 54 of 118 (45.8%) patients became symptom free or had 1 attack or less per year. In almost all of the other patients the disease became milder. The frequency of acute attacks was reduced to 16.2% of the pretreatment number. Adverse events (weight gain, virilization, menstrual irregularities, headache, depression, and/or liver abnormalities) were noted in 98 patients, but in general were mild and the drug was withdrawn in 30. Because the drug was developed as a contraceptive, many of these are not true side effects but relate to the expected physiologic action of the drug. Interestingly, most of the patients who discontinued the drug because of side effects did so in the first 2 years after treatment was started. A more recent study of the German and Hungarian experience makes other interesting points.¹⁴ It is pointed out that some individuals with borderline hypertension may become hypertensive on danazol treatment. Marked differences were found between the German and Hungarian cohort. The German's had 3 times the number of abdominal attacks when compared with the Hungarians and the Hungarians had more laryngeal attacks. Danazol did not become less effective over time in the German cohort and did become somewhat less effective in the Hungarians. It is this investigators' unpublished experience that if danazol becomes less effective over time, treatment can be discontinued for several months and that the drug will be more effective again when it is restarted.

As mentioned earlier, there are many side effects associated with danazol therapy and most of these side effects are associated with the other attenuated androgens as well.¹⁵ Almost all patients note weight gain and many patients have lipid abnormalities.^{16,17} Plasma low-density lipoprotein and cholesterol have been noted to be increased and high-density lipoprotein (HDL) levels to fall. One study suggests that the incidence of atherosclerosis rises, but the study only presents data on lipid levels, which are in keeping with such a suggestion.¹⁷ Because the patients are on these agents for prolonged periods, these are not minor complications. In a more limited but much more complete study of lipids in 17 patients who were on danazol for an average of more than 2 years at an average dose of 170 mg/d compared with controls, the effects were less impressive.¹⁸ It was pointed out that the values in this study were corrected for body mass index, a correction not applied in earlier studies. There were no changes in HDL-cholesterol or carotid intima-media thickness in this study. On the other hand, patients had signs of coagulation pathway activation.

Some patients develop liver function abnormalities with abnormal liver enzymes on androgen therapy. There is considerable variation from study to study. For example, in a long-term study of 70 Italian patients with HAE, no significant liver abnormalities were noted.¹⁶ On the other hand, in a handful of patients liver cysts or carcinomas have been reported. Some patients develop myopathies, hematuria, headaches, abnormal menses, increased or decreased libido, hair loss or gain, or anxiety reactions. In general, all of these side effects are quite mild and it is unusual for patients to come off danazol therapy because of side effects.¹⁹ Nevertheless, the side effect list is long and of concern. When patients are treated, the dose is progressively lowered until patients are having occasional attacks, because the severity of the side effects is dose-related.

The patient's clinical signs and symptoms must be followed carefully, but the levels of blood proteins like C1 inhibitor and C4 are not used to determine clinical effectiveness. It must be noted that impeded androgens are not effective in some patients.

They usually are not used in children because of the possibility of premature closure of the epiphyses but there are studies of danazol and oxandrolone use in childhood.^{20,21} They are not used in pregnancy, particularly in the first trimester, because of the danger of masculinization of the fetus. They are ineffective in some people. In addition, there are no intramuscular or intravenous (IV) preparations. Testosterone itself is not effective. The drugs must be given orally, and if a patient is having an abdominal attack with edematous gastrointestinal mucosa, the drugs may not be absorbed. Although the androgens are useful in prophylaxis, they are not useful in acute therapy. They do not have maximal effect for about 48 hours.

For all of these reasons, it was important that other forms of therapy be developed that have fewer side effects and be useful in all patients. There was a long history of using plasma-purified C1 inhibitor to treat acute HAE attacks and attention turned back to this agent for both acute treatment and prophylaxis.

C1 INHIBITOR USE IN PROPHYLAXIS

Three independent groups began the process of purifying C1 inhibitor from pooled plasma of thousands of donors in the mid 1970s. All 3 groups had extensive experience in purifying gamma globulin from plasma and had available facilities for processing plasma in large quantities. The Dutch Red Cross in the Netherlands, Behring Pharmaceuticals in Germany, and the American Red Cross in the United States all successfully purified the protein. C1 inhibitor was reported effective in treating HAE attacks in studies of all 3 products. Gadek and colleagues¹⁰ reported on the biochemical effect of the American Red Cross C1 inhibitor on C1 inhibitor and C4 blood levels in 8 patients with HAE in 1980 and showed that in 5 patients who were having attacks at the time of infusion, the agent terminated the attacks. Agostoni and Cicardi studied the Dutch Red Cross product and reported that it was effective in terminating an attack.²² It is this product that in a modern version has been approved for prophylaxis in the United States. Similarly, Bork studied the CSL Behring product and showed that it was effective in anecdotal report.²³ All of the early studies relied on historical experience to determine effectiveness of the agents, and it was important that a double-blind study to compare C1 inhibitor to placebo be performed in this highly variable disease. Such a study was reported by Waytes and colleagues²⁴ in 1996. This study compared with placebo yet another C1 inhibitor product prepared by Immuno of Austria. They reported the effectiveness both in terminating attacks and, in an inpatient portion of the study, in prophylaxis of disease. In the prophylaxis part of the study, they showed in 6 patients with severe disease who had not responded to conventional treatment that this agent given at 25 units/kg every 3 days for a total of 5 infusions was highly effective in prophylaxis. They followed the blood level of C1 inhibitor and C4 over the entire period of treatment. Blood levels of C1 inhibitor rose to normal immediately following infusion and by 3 days after infusion were again markedly depressed, illustrating the short half life of this plasma protein. As in earlier studies, the blood levels of C4 came back to normal more slowly, but then remained normal for the duration of the study. Placebo infusions did not affect either C1 inhibitor or C4 levels. Patient's attacks decreased by 60% compared with placebo but interestingly they did not decrease to zero.

The CSL Behring product, Berinert, was first licensed in Germany in 1985 and has been approved or licensed in Europe since that time. The Dutch Red Cross serum protein purification laboratory was merged into Sanquin in 2003. In 1989 heat treatment was added and more recently nanofiltration was added to further ensure sterility. These 2 products have been available in Europe for acute treatment of HAE attacks

for several decades and, although they were never studied in a double blind fashion, many reports attest to their effectiveness. They were never approved by the US FDA and they were never available in the United States. With the onset of the AIDS epidemic in 1980, the American Red Cross turned its attention away from HAE and their C1 inhibitor product was no longer made.

TRIALS OF THE CURRENTLY APPROVED C1 INHIBITOR PREPARATION

In 2008, nanofiltered, plasma-derived C1 inhibitor distributed by ViroPharma was approved for prophylaxis of patients with frequent or severe attacks. A relatively similar C1 inhibitor preparation prepared by CSL Behring was approved a year later for treatment of acute attacks. Other reviewers will discuss therapy for acute disease, but it should be remembered that C1 inhibitor is a physiologic protein that controls many mediator systems in blood. It is capable of down-regulating clotting factor XIIa and plasmin generation as well as kallikrein generation and complement activation. Under normal circumstances, the protein prevents untoward generation of bradykinin by down-regulating activation of the kinin generating system. The only currently available agent that has been studied in a controlled prophylaxis trial is the Dutch Red Cross agent, now imported by the pharmaceutical company ViroPharma and sold under the brand name Cinryze.²⁵ The prophylaxis portion of the trial followed a blinded trial of acute therapy. Patients had a preliminary screening visit to establish their diagnosis as types 1 or 2 HAE and then participated in an acute treatment trial. Following this portion of the study and, while the patients were still blinded with respect to the drugs they had received, they entered the prophylaxis trial. The placebo controlled trial that was conducted was a double-blind cross-over study in which patients received either C1 inhibitor at 1000 units or placebo intravenously every 3 to 4 days for a 12-week period and then crossed over for an additional 12 weeks to receive the alternate agent. If patients on any agent had an angioedema attack, they were eligible to receive in an unblinded fashion 1000 units of C1 inhibitor as rescue medication and they then resumed the study. The drug proved effective at decreasing attack frequency and duration as well as attack severity, and the number of open label rescue therapy treatments was markedly reduced in patients receiving drug compared with placebo (**Fig. 1**). Side effects were minimal. The study confirmed that psychological factors have a major effect on attack frequency in HAE. An interesting patient in the prophylaxis study actually had more attacks during treatment with Cinryze than on prophylaxis because of difficult events in her life. When her life became more normal, her attack frequency decreased markedly. It is interesting that HAE patients in all double-blind trials tend to have a higher attack frequency than those being treated with known effective agents. When the patient is perfectly confident that the agent will terminate attacks, their response rate is markedly higher. These factors must be kept in mind in considering treatment regimens in patients with HAE. In October of 2008, Cinryze was approved by the FDA at 1000 units IV bi-weekly for prophylaxis.

THEORETICAL PROBLEMS AND ADVANTAGES

All plasma products have a risk of infection. The risk is certainly minor with currently available C1 inhibitor products because they have been used in Europe for decades and no infection has been observed. Both start with the blood from healthy American donors and go through potent virus reduction purifications. At present, C1 inhibitor is administered IV, which is a disadvantage. Both CSL Behring and ViroPharma are examining the use of subcutaneous (SQ) injection of C1 inhibitor. As this product becomes available it should have the advantage of providing more stable blood levels of

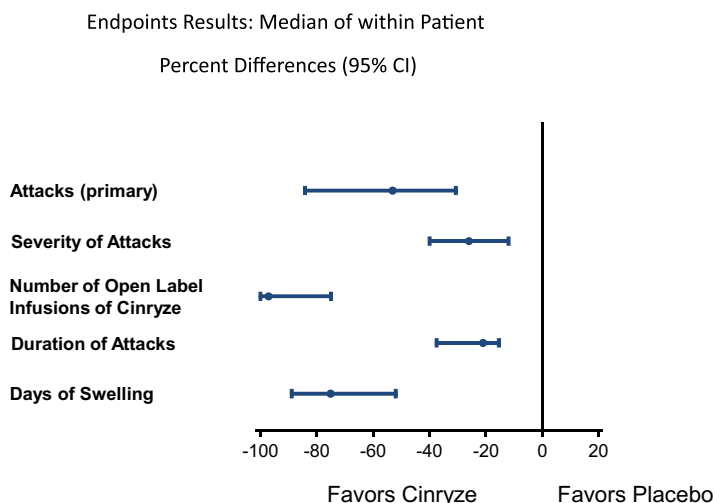


Fig. 1. The effectiveness of Cinryze prophylaxis in preventing HAE attacks. Shown is the statistical analysis of the activity of Cinryze in decreasing attack frequency, severity, duration, days of swelling, and open-label rescue treatments in the prophylaxis study. The effect is marked but as in other studies attack frequency did not decrease to zero.

protein and be more convenient to use. They may be more effective than the IV product which, because of its relatively short half life, does not maintain normal levels, even if administered every 3 to 4 days. Rate of absorption is a rate-limiting step in the use of SQ C1 inhibitor and the ViroPharma product is being studied with added hyaluronidase to improve absorption. Because patients are all heterozygotes and synthesize some normal C1 inhibitor, allergy to the administered product is unlikely. Because this is the normal physiologic protein, presumably it will provide normal physiologic regulation.

SHORT-TERM THERAPY

As mentioned earlier, there are circumstances where it is important to prevent attacks. It is both the patient experience and is reported that laryngeal attacks may follow tooth extraction.¹³ Fresh frozen plasma (FFP) as a source of C1 inhibitor has been recommended for the treatment of acute attacks.²⁶ We do not recommend FFP for treatment of acute attacks although it is clear that the vast majority of patients do note termination of attacks. FFP supplies high-molecular-weight (HMW) kininogen and prekallikrein, 2 proteins that are consumed during kinin generation. The cleavage of administered HMW kininogen in some patients generates additional bradykinin. The supply of fresh substrate for kinin generation may make attacks worse before the attack starts to resolve and the authors have seen patients develop more severe angioedema following FFP. Nevertheless, when the patient is not having an angioedema attack, it is safe to give FFP, we and others have reported on its use in dental and other types of surgery.^{27,28} Two units of FFP in our hands have prevented all acute angioedema attacks. Others have advocated 1 week of attenuated androgen therapy starting 1 week before these procedures. Androgens like danazol, even when used at high dose, usually have minimal side effects if only used for a week and these disappear rapidly. They have been used successfully before dental and surgical procedures.²⁹ Obviously, the new C1 inhibitor preparations also provide protection in

these situations. In providing the deficient protein, while being free of kinin substrates, these agents are ideal for preventing attacks. In every case, products should be made available that reliably terminate unexpected acute attacks.

SUMMARY

In the period of one professional lifetime, the field has gone from an incomplete clinical picture of the syndrome to a complete clinical picture, to an understanding of the gene defect and the pathophysiology of the disease, and to having drugs available for acute therapy and for prophylaxis that bring this disease under control. The lot of patients with HAE is markedly improved.

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