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Reviews

Long-term prophylaxis therapy in patients with hereditary angioedema with C1 inhibitor deficiency

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Key Messages

- Treatment guidelines for long-term prophylaxis therapy of patients with hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) have changed over time; earlier guidelines were based on the number of attacks per month or days of disability, whereas recent guidelines suggest that such thresholds are arbitrary and treatment decisions should be individualized.
- Because the benefit-risk profiles and treatment burdens of C1-INH-HAE prophylaxis therapies have improved over time, it is possible that a broader group of patients may be candidates for prophylaxis therapy in the future.
- Prophylaxis therapy should be discussed as a potential treatment option for each patient with C1-INH-HAE.
- The decision to use prophylaxis medication for C1-INH-HAE will depend on each patient's individual needs and the course of their symptoms, with the goal of reducing the overall burden of disease and improving quality of life.

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ABSTRACT

Objective: To review the criteria for long-term prophylaxis therapy in patients with hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE), describe how these criteria have evolved over time, and anticipate how criteria may change in the future with the availability of new C1-INH-HAE treatment options.
Data Sources: Treatment guidelines, consensus statements, and expert reviews.
Study Selections: Manuscripts that described long-term prophylaxis therapy in patients with C1-INH-HAE were selected.
Results: Historically, patients with C1-INH-HAE were considered to be candidates for long-term prophylaxis therapy if they had at least 1 attack per month, had at least 5 days of disability per month because of C1-INH-

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HAE, or did not sufficiently respond to on-demand treatment. More recently, guidelines and reviews state that thresholds of number of attacks or days of disability are arbitrary and that treatment plans should be individualized to the patient's needs. Furthermore, all patients should have a comprehensive management plan that is reviewed periodically and should have at least 2 doses of on-demand treatment available. Prophylaxis therapy should be discussed as a potential treatment option for each patient; however, the decision for its use will depend on the patient's individual needs and the course of their symptoms.

Conclusion: The criteria for long-term prophylaxis therapy in C1-INH-HAE have changed with the recognition that treatments should be individualized to the patient's needs and with the availability of new medications that have more favorable benefit-risk profiles, are easier to use, and improve patients' quality of life.

Introduction

Hereditary angioedema with C1 inhibitor (C1-INH) deficiency (C1-INH-HAE) is a rare condition that may have a profound effect on patients' lives, both physically and emotionally.[1,2] Swelling can occur in the abdomen, face, throat, genitalia, or extremities and may cause pain and disability. Abdominal swelling can cause severe pain and potentially intestinal obstruction, incapacitating the patient during the attack. Swelling of the extremities can impede patients from walking or using their hands, and swelling with airway involvement is potentially life-threatening.[3] The pain and disability caused by attacks may inhibit patients' ability to conduct their normal activities of daily life, including attending work or school. Attacks are unpredictable, making it difficult for patients to plan for travel or other life events, and often cause anxiety about future attacks.[4] C1-INH-HAE is an autosomal dominant disorder, and parents with the condition may have concerns about having children or passing it on to their children.[4]

There is frequently a delay in the time between symptom onset and confirmed diagnosis in patients with C1-INH-HAE.[5,6] Without a proper diagnosis, patients may spend years without appropriate therapy and are at risk for a potentially life-threatening airway attack.[3] In addition, misdiagnosed patients may receive unnecessary and ineffective treatment or surgical procedures.[7,8] Furthermore, even after a proper diagnosis, patients may have inadequate or suboptimal therapy because of the rarity of the disease.

Treatment strategies include short-term (on-demand) or prophylaxis therapy.[9-13] The goal of short-term treatment is to minimize the duration and severity of an angioedema attack that has started. Short-term or preprocedural prophylaxis treatment is administered before an event that is expected to trigger an angioedema attack, such as a medical or invasive dental procedure. The goal of long-term prophylaxis treatment is to prevent attacks or reduce their severity if they occur.

Since the early 2000s, treatment guidelines and expert reviews have described criteria used to identify patients with C1-INH-HAE who would be candidates for long-term prophylaxis therapy. The purpose of this review is to describe how these criteria have evolved over time and may change in the future.

Current Treatment Options

All patients with C1-INH-HAE should have access to at least 2 doses of short-term or on-demand medication.[13] The US Food and Drug Administration (FDA)–approved on-demand treatment options include intravenous plasma-derived C1-INH (Berinert), intravenous recombinant C1-INH (Ruconest), subcutaneous bradykinin B2-receptor antagonist (icatibant [Firazyr]), and subcutaneous plasma kallikrein inhibitor (ecallantide [Kalbitor]). Fresh frozen plasma may be used if these agents are not available, but the efficacy of fresh frozen plasma has not been evaluated in controlled studies, and it has been hypothesized that fresh frozen plasma may rarely exacerbate angioedema attacks in some patients[14,15]; therefore, it should be used with caution.

Patients who are only receiving on-demand treatment may require short-term prophylaxis before surgical or invasive dental procedures or stressful life events that may trigger an attack. Although several observational studies have been conducted,[16,17] there is a lack of controlled studies evaluating treatments for short-term prophylaxis,[11,12] and no drugs are approved for this indication in the United States. Despite this, the most recent guidelines from the United States recommend intravenous C1-INH 1 to 12 hours before the procedure.[13,15] Intravenous plasma-derived C1-INH formulations are approved in Europe and recommended by international consensus guidelines (dose of 10-20 U/kg or 1,000 U 1-6 hours before the procedure).[12] High-dose androgens (200 mg of danazol equivalent 3 times daily for 5 days before the event and 2 days after)[18] or fresh frozen plasma (2 U 1 to 2 hours before the procedure)[14] are used when C1-INH is not available or contraindicated but are secondary recommendations.

Long-term prophylaxis therapies are summarized in Table 1. Antifibrinolytics are used outside the United States at higher frequencies but are not approved by the FDA for use in patients with C1-INH-HAE in the United States, and many patients do not respond to them. Overall, the efficacy of antifibrinolytics appears to be less than other prophylaxis treatment options, but formal comparison studies have not been performed.[12] Androgens are effective but have adverse effects, such as virilization in women, mood changes, acne, weight gain, and elevations in lipid levels.[19-21]

Human plasma-derived C1-INH is available for long-term prophylaxis treatment in intravenous and subcutaneous formulations. Intravenous C1-INH was approved in the United States in 2008 for routine prophylaxis in adult and adolescent patients. In a randomized, placebo-controlled, crossover study (n = 22),[22] the mean number of attacks decreased approximately 50% while patients were receiving 1,000 U of intravenous C1-INH every 3 or 4 days during a 12-week treatment period compared with placebo (mean, 6.26 vs 12.73 attacks per treatment period; $P < .001$). Dose escalation of intravenous C1-INH was evaluated in an open-label study of patients whose conditions were not adequately controlled with the 1,000-U dose.[23] In this study, doses up to 2,500 U every 3 or 4 days were well tolerated, and 14 of 20 patients (70%) were successfully treated or had a reduction from the historical attack rate of more than 1 attack per month while receiving higher doses.

Subcutaneous C1-INH was approved in the United States in 2017 for routine prophylaxis in adult and adolescent patients. In a randomized, placebo-controlled, crossover study,[24] patients receiving the approved dose of 60 IU twice weekly during a 16-week treatment period (n = 45) had a median reduction in attack frequency of 95% compared with placebo (mean, 0.52 vs 4.03 attacks per month; $P < .001$). In both intravenous and subcutaneous studies, prophylaxis treatment with plasma-derived C1-INH was well tolerated.

Several compounds are in the later stages of clinical development for routine prophylaxis in patients with C1-INH-HAE, including recombinant C1-INH (administered intravenously),[25,26] a monoclonal antibody to kallikrein (administered subcutaneously [lanadelumab]),[27,28] and a plasma kallikrein inhibitor (administered orally

Table 1
Summary of Treatments for Long-Term Prophylaxis

Agent	Route of administration	Dosage	Approved indication
Androgens	Oral	Adults: 200 mg/d of danazol equivalent or less	Prevention of angioedema attacks
		Children: 2.5-5 mg/kg daily of danazol equivalent not exceeding 200 mg/d	Not approved by the FDA; not recommended before Tanner stage V[37]
Antifibrinolytics	Oral	Adults: 30-50 mg/kg daily of tranexamic acid equivalent	Not approved by the FDA; recommended only when C1 inhibitor concentrate not available and androgens contraindicated[51]
		Children: 20-40 mg/kg daily of tranexamic acid equivalent	Not approved by the FDA; recommended only when C1 inhibitor concentrate not available[51]
C1 esterase inhibitor (human)	Intravenous	Adults and adolescents: 1,000-2,500 U every 3 or 4 days	Routine prophylaxis in adolescents and adults
		Children: 10-20 U/kg twice weekly	Not approved by the FDA
C1 esterase inhibitor subcutaneous (human)	Subcutaneous	Adults and adolescents: 60 IU/kg twice weekly	Routine prophylaxis in adolescents and adults
		Children: Unknown	Not approved by the FDA

Abbreviations: FDA, US Food and Drug Administration.

[BCX7353]). In a randomized, placebo-controlled, crossover study (n = 32),[25] patients receiving 50 IU/kg of recombinant C1-INH twice weekly for a 4-week treatment period had a mean reduction in attack frequency of 63.3% compared with placebo (mean, 2.7 vs 7.2 attacks per treatment period; $P < .001$). In a randomized, placebo-controlled, parallel-group trial,[28] patients receiving 300 mg of lanadelumab every 2 weeks for 26 weeks (n = 27) had a mean reduction in attack frequency of 86.9% compared with placebo (n = 41) (mean, 0.26 vs 1.97 attacks per month; $P < .001$). Interim results from a phase 2, randomized, placebo-controlled, parallel-group trial showed that patients receiving the oral plasma kallikrein inhibitor once daily for 4 weeks (n = 14) had a 52% reduction in attack frequency during weeks 2 to 4 compared with those in the placebo group (n = 14) (least-squares mean, 0.436 vs 0.911 attacks per week; $P = .04$).[29]

Prophylaxis Treatment

Historical Perspective

Treatment guidelines, consensus statements, and expert reviews that describe criteria for identifying patients who may be candidates for prophylaxis therapy are summarized in Table 2. This review does not address specific considerations for prophylactic treatment of women and children, but these topics are addressed elsewhere.[9,30-38] The first criteria for long-term prophylaxis were described in a 2003 Canadian consensus statement,[39] a 2004 review from the C1-INH Workshop (a meeting of experts that is conducted in Budapest, Hungary, every 2 years),[40] and a 2004 international consensus guideline developed by experts from Canada and Hungary.[41,42] These criteria stated that patients with at least 1 attack or severe event per month or 5 days or more of disability per month would be candidates for long-term prophylaxis therapy. Guidelines from the United Kingdom published in 2005[43] added that patients who do not sufficiently respond or do not have access to on-demand treatment may also be candidates for long-term prophylaxis therapy.

In 2009, a review written by several of the authors of this manuscript suggested that other criteria should be considered besides attack frequency and days of disability.[44] The reasons for this are related to the clinical course of C1-INH-HAE and the effect of the condition on patients' lives. Attack severity is unpredictable and is not related to attack history—even patients with infrequent attacks are at risk of a severe attack at any time. In addition, patients who have experienced infrequent but severe attacks that involve the airway or require hospitalization may wish to take medication to prevent such events from recurring. Finally, some patients may not consider 5 days per month to be an acceptable amount of disability. Therefore, these authors recommended that treatment plans be individualized to the patient's needs and that prophylaxis therapy may be warranted in a wider variety of patients. They suggested that other criteria could be used in the decision to initiate prophylaxis treatment, such as rapidity of attack onset, access to care, history of laryngeal attacks, prior visits to emergency department or intensive care unit, intubation, missed days of school or work, anxiety, impaired quality of life, effect on lifestyle, and analgesic dependency.[44]

In a lecture published in 2011 about C1-INH-HAE and treatment that went "beyond international consensus,"[45] Tom Bowen, MD, advocated for an individualized approach to treatment. He stated that thresholds of number of attacks per month or days of disability are arbitrary and that patients should not be required to have failed androgen therapy to be candidates for prophylaxis with plasma-derived C1-INH therapy. He proposed that treatment of other chronic genetic diseases can be used as a model for C1-INH-HAE. For example, in hemophilia and immunodeficiency, the goal of treatment is to normalize patient's life not just to treat individual bleeding or infection events. Dr Bowen suggested that these principles should be applied to treatment of patients with C1-INH-HAE, taking into account costs and evidence of benefits and risks. Concurrently, reviews of prophylaxis therapy from an international group[46] and a group from the United States[47] endorsed an individualized treatment approach that takes into account the patient's disease burden, quality of life, and response to previous treatments.

In 2012, three major international consensus statements[11,12,48] on treatment of patients with C1-INH-HAE were published using evidence-based criteria to evaluate treatments that had recently been approved by regulatory authorities. The Hereditary Angioedema International Working (HAWK) group[11] stated that treatment should be individualized to patients' needs with the goal of normalizing quality of life, on-demand treatment may be sufficient to reduce burden of disease, and long-term prophylaxis is appropriate for patients who are inadequately treated by on-demand therapies. However, the HAWK group could not reach consensus on what constituted inadequate treatment. A few panel members defined it using criteria consistent with prior consensus guidelines (ie, >24 days per year with symptoms or >12 severe attacks per year).

The World Allergy Organization (WAO) guidelines did not include threshold of severity for patients to qualify for prophylaxis treatment, stating that it should be considered for severely symptomatic patients, taking into account multiple factors, such as the severity of disease, frequency of attacks, patient's quality of life, availability of resources, and failure to achieve adequate control by appropriate on-demand therapy.[12] The International Collaboration in Asthma, Allergy, and Immunology (iCAAL) guidelines stated that patients who

Table 2
Summary of Criteria From Consensus Guidelines and Expert Reviews on the Use of Long-Term Prophylaxis Therapy in Adults With Hereditary Angioedema Due to C1-INH Deficiency

Year	Document	Criteria
2003	Canadian consensus	Disabled >5 days per month
2004	Third C1-INH Deficiency Workshop[40]	>1 Attack per month (or a life-threatening episode in children)
2004	Canadian international consensus[42]	>1 Severe event per month or disabled >5 days per month
2005	UK consensus[58]	1 Episode of severe abdominal pain in 1 year or any head or neck swellings, frequent peripheral or genital swellings, or a requirement for concentrate more than once a year
2008	Canadian-Hungarian consensus[41]	>1 Severe event per month or disabled >5 days per month
2009	US expert review on prophylaxis[44]	Criteria in addition to frequency of attacks and days of disability should be considered (see text for detail)
2010	Canadian approach[59]	>1 Severe event per month or disabled >5 days per month
2011	Canadian expert review—beyond consensus[45]	Thresholds of number of attacks or number of days of disability are arbitrary; treatment should be individualized
2011	Spanish consensus[60,61]	Edema of the glottis, >1 edema episode per month, >1 severe abdominal attack, >1 severe cervicofacial attack, altered quality of life
2011	International expert review on prophylaxis[46]	Frequent or severe attacks, laryngeal attacks, significant anxiety, poor quality of life, or limited access to emergency care
2012	US expert review on prophylaxis[47]	Individualized treatment
2012	HAWK guidelines[11]	On-demand therapy inadequate to minimize adverse effects related to the disease; no consensus on when on-demand should be considered to be inadequate Substantial minority: >12 severe attacks per year or >24 days per year affected by hereditary angioedema
2012	WAO guidelines[12]	Severely symptomatic patients taking into consideration the severity of disease, frequency of attacks, patient's quality of life, availability of resources, and failure to achieve adequate control by appropriate on-demand therapy
2012	iCAALL guidelines[48]	Patients not treated successfully with on-demand therapy; take into account attack frequency and severity, access to acute care, comorbidities, and patient circumstances and preferences
2013	ACAAI and AAAAI Joint Task Force on Practice Parameters[15]	Patients not treated successfully with on-demand therapy; individualize treatment based on patient's situation; consider attack frequency, attack severity, location of attacks, access to acute care, comorbid condition, and patient preference
2013	US HAEA MAB guidelines[13]	Individualized treatment should not be based on rigid criteria
2014	Canadian consensus[49]	On-demand treatment does not sufficiently meet patient treatment requirements; should not be based on arbitrary threshold of attack frequency
2016	German expert review on prophylaxis[50]	Individualized treatment; when on-demand therapy is administered as frequently as prophylaxis therapy or insufficiently controls disease
2018	WAO-EAACI guidelines[51]	Individualized treatment; patients should be evaluated for long-term prophylaxis at each visit

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; C1 INH, C1 inhibitor; HAWK, Hereditary Angioedema International Working Group; iCAALL, International Collaboration in Asthma, Allergy, and Immunology; US HAEA MAB, US Hereditary Angioedema Association Medical Advisory Board; WAO, World Allergy Organization.

are not treated successfully with on-demand therapy are candidates for long-term prophylaxis and that the decision for prophylaxis treatment may take into account attack frequency and severity, access to acute care, comorbidities, and patient circumstances and preferences.[48]

The most recent guidelines for the United States include practice parameters from a joint task force representing the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology[15] and a statement written by the US Hereditary Angioedema Association Medical Advisory Board (US HAEA MAB).[13] The practice parameters stated that patients are candidates for long-term prophylaxis if they are not managed successfully with on-demand therapy.[15] They also stated that treatment should be individualized based on the patient's situation, and factors such as attack frequency, attack severity, location of attacks, access to acute care, comorbid conditions, and patient preference could be considered in the decision to use long-term prophylaxis. In addition, the need to start or continue prophylaxis should be reviewed periodically because disease severity may change over time. The US HAEA MAB had similar recommendations but also stated that a comprehensive management plan should be established for each patient.[13] The ultimate goal of the management plan is to reduce the morbidity and mortality caused by C1-INH-HAE to improve patients' quality of life. They also stated that decisions for prophylaxis treatment should not be based on rigid criteria but rather based on the needs of the individual patient.

The most recent Canadian guidelines[49] and recommendations from German experts[50] are consistent with the US HAEA MAB in stating that no rigid criteria should be used in the decision for prophylaxis treatment. They are also consistent with HAWK consensus, US practice parameters, and iCAALL guidelines in stating that prophylaxis is warranted for patients in who are not adequately treated with on-demand therapy only.

The most recent international guidelines are the 2017 revision and update from the WAO in collaboration with the European Academy of Allergy and Clinical Immunology.[51] These guidelines recommend that patients should be evaluated for long-term prophylaxis at every visit with the treating physician, and the need for prophylaxis should be based on the disease burden and patient's preference, with the outcome of minimizing the patient's burden of disease.

Current Perspectives and Future Trends

The historical review above shows that the clinical considerations for prophylaxis therapy have changed in recent years from rigid criteria of numbers of attacks or days of disability to an individualized approach, taking multiple factors into account. Guidelines also vary by global region, accounting for local treatment practices and availability of medications. International guidelines must take a global perspective and incorporate these regional differences in treatment practices and regulatory approvals.

C1-INH-HAE is a multifaceted condition that affects each patient differently and even the same patient over time. Patients with more severe disease require more treatment to reduce morbidity and the risk of mortality. Disease severity should be evaluated in the context of effect on quality of life and ability to conduct

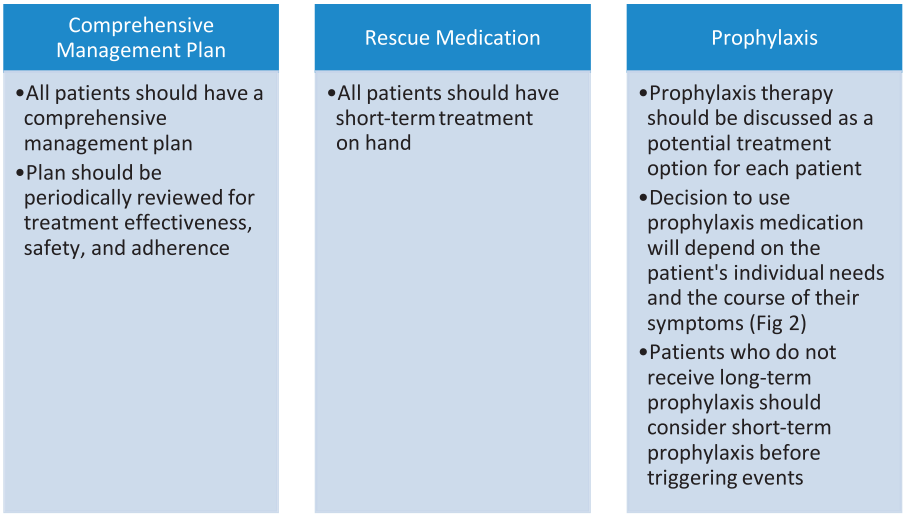

Figure 1. Recommendations for the therapeutic management of patients with hereditary angioedema due to C1 inhibitor deficiency.

activities of daily living. Thresholds of attack numbers, days of disability, or hospitalizations are arbitrary and not necessarily indicative of the effect of the disease to the individual patient. When early treatment guidelines for prophylaxis therapy were developed, the most common medications were androgens and antifibrinolytics, and on-demand treatments were not approved or available in the United States. Before regulatory approval in 2008, plasma-derived C1-INH was not available as a long-term prophylaxis therapy, and the efficacy and safety of this treatment had not been rigorously studied.

Since then, studies of intravenous plasma-derived C1-INH for long-term prophylaxis provided evidence for the efficacy and safety[22,23,52] and effect on quality of life,[53] and many patients have benefited from the use of this therapy. However, there is a treatment burden associated with any intravenously administered medication. Some patients may be unable or unwilling to access veins for administration. Patients with venous access problems may use subcutaneous ports, which are associated with risks of infection and thrombosis.[13,23,54] In addition, some patients receiving intravenous C1-INH have breakthrough attacks,[55] and some require higher doses than the originally approved dose of 1,000 U.[23] Dose escalation to improve efficacy is associated with additional cost.

The availability of effective on-demand treatments that can be self-administered has been a major advance in the care of patients with C1-INH-HAE.[50] If attacks are treated early, the overall duration and severity are greatly reduced, which improves the overall morbidity and risk of mortality. Some patients use this strategy to effectively manage their disease without incurring the risks of long-term androgen therapy or the treatment burden of frequent scheduled intravenous administrations of C1-INH.

However, new prophylactic therapies with improved efficacy, a more favorable benefit-risk profile, and a reduced treatment burden may change the considerations for prophylaxis therapy. Subcutaneous therapies obviate the need for venous access and likely reduce the treatment burden compared with intravenous administration. Development of a safe and effective oral therapy would meet a major unmet need in ease of treatment administration. With these improvements in therapeutic options, the treatment burden of prophylaxis therapy will likely decrease. Patients who previously elected to manage their disease solely by treating attacks with on-demand therapy may now consider prophylaxis approaches based on quality of life benefits demonstrated in recent studies.[56]

Recommendations for the Therapeutic Management of Patients With C1-INH-HAE

In the absence of a cure, the goal of treatment is to minimize the burden of illness on patients and enable them to lead normal lives. For patients with C1-INH-HAE, this means reducing the risk of potentially fatal and disabling angioedema attacks, minimizing the duration and severity of attacks when they occur, and minimizing the risks and burdens of treatment. Health care professionals should consider any available treatment to achieve these goals according to the following principles (Fig 1).

First, all patients should have a comprehensive management plan that should be reviewed periodically for treatment effectiveness, safety, and adherence.[13,57] Second, all patients should have on-demand treatment on hand regardless of whether they are receiving prophylaxis therapy because even patients receiving the most effective prophylaxis therapies are at risk of having an attack.[11-13] Third, prophylaxis therapy should be discussed as a potential treatment option for each patient. The decision to use prophylaxis medication will depend on the patient's individual needs and the course of their symptoms (Fig 2).

The overall burden of disease should be considered in the decision to start prophylaxis therapy. This burden can be

Figure 2. Factors to consider when developing the treatment plan.

characterized by a variety of factors. Clinical aspects of disease activity, such as attack frequency and severity and history of severe debilitating or life-threatening attacks, may be considered, as well as access to urgent care in case one of these severe attacks occurs. However, other components of disease burden may also be considered. Patients with constant fear and anxiety about future attacks may warrant prophylaxis therapy. In addition, patients who miss work or school, are unable to plan future life events (eg, vacation, marriage, holidays, and children), or are unable to conduct activities of daily living (eg, holding utensils and implements, walking, driving, exercising, childcare, and eldercare) may also warrant prophylaxis therapy. Finally, the benefit-risk profile and treatment burden of available therapies should be considered in the decision for prophylaxis. This not only includes weighing the evidence for safety and efficacy and considering the route of administration but also estimating the risk of breakthrough attacks and the requirements for acute rescue medication.

The idea that prophylaxis therapy should be discussed with all patients does not mean that all patients will be treated with prophylaxis therapy. Even with the availability of highly effective and safe prophylaxis therapies, some patients may prefer to manage their disease by treating individual attacks with on-demand therapy. Patients who are not receiving long-term prophylaxis should receive short-term prophylaxis before events or circumstances that are expected to trigger an attack, such as surgery or invasive dental work, and some may also consider it before or during stressful life events.

Conclusion

A comprehensive and individualized treatment approach is the best way to reduce the morbidity and mortality risk associated with C1-INH-HAE. In past years, the treatment paradigm was based on treating individual attacks. Long-term prophylaxis therapy was considered primarily for patients whose conditions were inadequately controlled by on-demand therapy alone. This approach is based on the inherent assumption that patients had access to safe and effective on-demand therapy and that the treatment burden, adverse effects, or cost associated with prophylaxis therapy potentially outweighed its benefit. With the availability of medications that have improved benefit-risk profiles and reduced burden of treatment, long-term prophylaxis therapy may be preferred by a broader group of patients because the substantial reduction in attacks results in a more predictable and symptom-free life. Such progress in treatment of C1-INH-HAE is consistent with advances in similar chronic conditions (eg, hemophilia) for which preventive therapy has replaced reactive treatment approaches and resulted in reductions in morbidity and improved quality of life.

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