CASE REPORT

Improving patient outcomes in hereditary angioedema: reducing attack frequency using routine prevention with C1 inhibitor concentrate

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SUMMARY

Hereditary angioedema (HAE) is a rare inherited disorder, characterised by recurrent oedema attacks in various regions of the body. In HAE, mutations in the C1 esterase inhibitor (C1-INH) gene result in decreased C1-INH concentrations (type I HAE) or functionally deficient C1-INH (type II HAE), leading to inappropriate activation of the kallikrein–kinin system and release of vasoactive mediators. Treatment of HAE aims to manage acute attacks (using replacement C1-INH or bradykinin B2 receptor antagonist) or prevent attacks through prophylaxis (using C1-INH or attenuated androgens). We present a case of a 67-year-old man with HAE who suffered a high number of breakthrough HAE attacks while undergoing long-term prophylaxis with attenuated androgens. Androgen therapy was safely discontinued and routine prevention therapy with C1-INH (1000 U) introduced as part of an individualised management approach, in line with published clinical trial data, which improved patient outcomes in terms of HAE attack frequency and severity.

BACKGROUND

Angioedema is a vascular reaction of the deep dermis or subcutaneous/submucosal tissues characterised by increased localised blood vessel dilation and permeability resulting in oedema, which may be mediated by mast cell mediators or bradykinin.[1–3] Bradykinin-mediated angioedema may occur either on an acquired or a hereditary basis due to a deficiency/defect of C1 esterase inhibitor (C1-INH). A number of acquired angioedemas also exist which are bradykinin-mediated, but not due to C1-INH. These include ACE inhibitor (ACE-I)-induced angioedema, affecting between 1 in 200 and 1 in 1000 patients treated with ACE-I.[4 5]

Hereditary angioedema (HAE), a rare autosomal dominant disorder affecting approximately 1 in 50 000 people, is characterised by recurrent subcutaneous or submucosal oedema attacks in various regions of the body.[4 6 7] In HAE, mutations in the C1-INH gene result in decreased C1-INH concentrations (type I HAE) or functionally deficient C1-INH (type II HAE), leading to inappropriate activation of the kallikrein–kinin system and release of vasoactive mediators. These mediators include the bradykinin responsible for symptomatic HAE attacks,[7–9] which can range in frequency from a few to over 100/year.[10 11] While HAE attacks vary in location and severity, those involving the upper airways are potentially life-threatening because of the danger of asphyxiation.[12] The differential diagnosis of the cause of angioedema involves careful anamnesis, physical examination and appropriate laboratory testing.[5] A diagnosis of C1-INH deficiency requires confirmation with measurement of C4 level (reduced in most C1-INH-deficient patients) and C1-INH antigenic and functional levels.[4 5]

Treatment of HAE aims to either manage acute attacks, or to prevent attacks using prophylaxis, and best clinical practice for these treatment paradigms is outlined in recent clinical guidelines.[4 5] In Europe, acute attacks are managed with plasma-derived C1-INH concentrates (Cinryze (C1 inhibitor (human), ViroPharma); 1000 U intravenously; Berinert (C1 esterase inhibitor (human), CSL Behring; 20 IU/kg intravenously)); recombinant human C1-INH (Ruconest (recombinant C1 esterase inhibitor (human), Pharming); 50 IU/kg intravenously) or bradykinin B2 receptor antagonist (Firazyr (Icatibant, Shire); 30 mg subcutaneously).[1] The approved long-term prophylactic treatments in Europe are C1-INH (Cinryze) and 17alpha-alkylated androgens (eg, danazol up to 200 mg per day), although the latter are approved in the USA and in only certain European countries for the treatment of HAE in patients >16 years of age.[4] These treatments are currently not approved by the relevant regulatory authorities for the treatment of ACE-I-induced angioedema. In addition, international guidelines (World Allergy Organization, 2012) state that antifibrinolytic agents, including tranexamic acid or epsilon aminocaproic acid, are not recommended for on-demand treatment of HAE attacks or long-term prophylaxis in HAE.[4]

CASE PRESENTATION

We report the case of a 67-year-old male patient, with no family history of HAE, who, following his first attack in 1992, was diagnosed with type I HAE in 1996, aged 49 years. This patient suffered with a high attack frequency (up to one attack per day), particularly in the head and neck region, although abdominal and cutaneous attacks were also reported. He was often hospitalised as a result of attacks for up to 1–2 days/week. Except for pre-existing hyperlipidaemia and disease of the cervical spine, which had prevented him working since 1994, the patient had no other comorbidities.

DIFFERENTIAL DIAGNOSIS

The patient's symptoms were initially misdiagnosed as allergic oedema. A correct diagnosis of type I

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HAE was made in 1996 following laboratory testing for C1 and C4 levels. Following testing, C1 concentration was 3.2 mg/dL (normal 15–35 mg/dL), C1 activity was 5% of normal and C4 concentration was 5 mg/dL (normal 20–50 mg/dL).

TREATMENT

Between 1996 and 1998 this patient was treated for acute attacks with C1-INH (20 IU/kg, 3–4 times per week). Subsequent attacks continued to be frequent and severe, requiring the introduction of danazol prophylaxis (200 mg/day) in 1998.

Attack frequency was reduced from every day to every other day and, initially, severe breakthrough attacks were treated with C1-INH (20 IU/kg; up to twice per week). Despite prophylactic treatment with danazol at the maximum recommended safe daily dose (200 mg/day), the patient continued to suffer a high frequency of breakthrough attacks (2–3 attacks/week). A higher dose of danazol (up to 400 mg/day) did not result in reduction in the attack rate of the patient. However, at this higher dose of danazol adverse events such as hypertension and elevated liver enzymes were observed.

Between 2009 and 2011, 245 breakthrough attacks, comprising 114 abdominal attacks, 75 head and neck attacks (including 19 laryngeal attacks) and 56 attacks of the genitalia or extremities occurred. Following regulatory approval (in 2008), the bradykinin receptor antagonist, icatibant (30 mg subcutaneously) was used to treat breakthrough attacks. Withdrawal of danazol from the German market over safety-related concerns, combined with the continuing high frequency of attacks while receiving androgen therapy, led to prophylactic treatment being changed to C1-INH (1000 U intravenously; twice weekly, every third day) in January 2012. Breakthrough attacks were again treated on-demand with icatibant (30 mg subcutaneously).

OUTCOME AND FOLLOW-UP

After switching prophylactic danazol treatment to routine prevention with C1-INH (1000 U intravenously), there was a significant reduction in acute HAE attacks to one or two per month. Furthermore, these were restricted to the abdomen or genitals (12 and 3 attacks, respectively), with swellings in the head and neck region being completely abolished (figure 1).

Approximately 80% of breakthrough attacks required acute treatment, as the patient felt breakthrough attacks to be milder while taking C1-INH routine prevention. Specifically, abdominal oedema appeared significantly milder and more responsive to acute therapy in the context of C1-INH routine prevention, compared with danazol prophylaxis.

To date, the patient has required no emergency hospitalisation since starting C1-INH routine prevention, only needing to attend routine outpatient appointments twice per year. In addition, he has made his first extended holiday for a number of years.

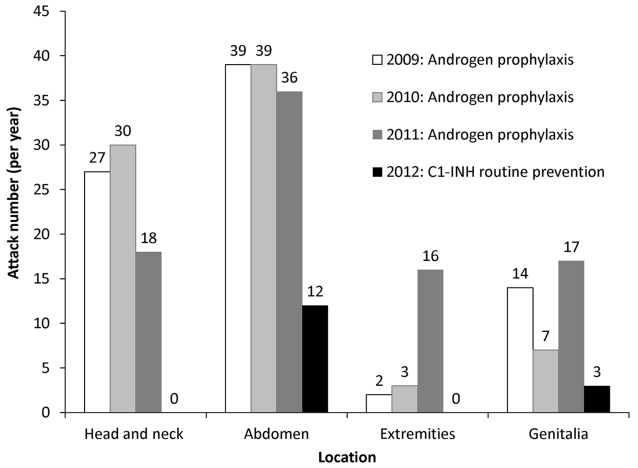

Figure 1 Breakthrough attacks treated during androgen prophylaxis (2009–2011) and during C1 esterase inhibitor routine prevention (2012). Breakthrough attacks were treated with icatibant (30 mg subcutaneously).

DISCUSSION

In managing the disease in this particular patient, we followed the dose recommendation and infusion intervals as reported in the literature.[13–15] Routine prevention with C1-INH (1000 U intravenously twice weekly, every third day) proved to be effective for the long-term prevention of HAE in a patient with severe HAE, manifested by high attack frequency despite prophylactic treatment with attenuated androgens and adjuvant on-demand therapy with bradykinin receptor antagonist. C1-INH routine prevention reduced attack frequency significantly, confirming previously reported data from pivotal trials of this treatment paradigm.[9 10] The appearance of potentially life-threatening oedema of the head and neck region was also abolished, suggesting a reduced potential risk of asphyxiation. In addition, the emergency utilisation of hospital resources was reduced while on C1-INH routine prevention. In line with recently reported data, discontinuation of androgen therapy and introduction of C1-INH (1000 U intravenously twice weekly) for routine prevention of HAE attacks resulted in improved outcomes. For this patient with frequent HAE attacks, the direct medical costs per annum (medication only) for twice-weekly routine prevention with C1-INH are comparable with on-demand treatment with icatibant for treatment of breakthrough attacks while taking danazol prophylaxis. C1-INH routine prevention may contribute to decreased costs associated with hospitalisation, as well as decreased indirect costs (loss of work and productivity) associated with HAE.

Learning points

- Hereditary angioedema (HAE) is frequently misdiagnosed and can be fatal if oedema attacks affect the upper airway. There is, therefore, a need for increased disease awareness to improve diagnosis.
- In this case study, a high rate of head and neck oedemas (daily) and increased potential for progression of swelling to the upper airway and risk of asphyxiation predispose this patient to potentially fatal outcomes.
- Prophylaxis with attenuated androgens provided a partial reduction in attack frequency. However, withdrawal of danazol from the German market due to potential side effects requires the use of non-androgen-based long-term prevention therapies for HAE.
- This case demonstrates that, in line with published clinical trial data:
  - Androgen therapy can be safely discontinued and routine prevention therapy with C1-INH (1000 U) introduced as part of an individualised management approach, utilising all available treatment options with improved outcomes in terms of HAE attack frequency and severity.
  - In the case of this patient, prevention therapy with C1-INH may also contribute to improved quality of life and reduced resource utilisation.

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REFERENCES

1 Bork K, Meng G, Staubach P, *et al*. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006; 119:267–74.
2 Longhurst HJ, Bork K. Hereditary angioedema: causes, manifestations and treatment. *Br J Hosp Med (Lond)* 2006;67:654–7.
3 Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol* 2005;53:373–88.
4 Craig T, Aygören Pürsün E, Bork K, *et al*. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J* 2012;5:182–99.
5 Lang DM, Aberer W, Bernstein JA, *et al*. International consensus on hereditary angioedema. *Ann Allergy Asthma Immunol* 2012;109:395–402.
6 Bowen T, Cicardi M, Bork K, *et al*. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol* 2008;100(1 Suppl 2):S30–40.
7 Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med* 2008;359:1027–36.
8 Donaldson VH, Evans R. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C1-esterase. *Am J Med* 1963;35:37–44.
9 Davis AE III. Hereditary angioedema: a current state-of-the-art review, III: mechanisms of hereditary angioedema. *Ann Allergy Asthma Immunol* 2008;100(1 Suppl 2):S7–S12.
10 Bernstein IL. Hereditary angioedema: a current state-of-the-art review, II: historical perspective of non-histamine-induced angioedema. *Ann Allergy Asthma Immunol* 2008;100(1 Suppl 2):S2–6.
11 Bork K, Hardt J. Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate. *Am J Med* 2009:122:780–3.
12 Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 2012;130: 692–7.
13 Zuraw BL, Busse PJ, White M, *et al*. Nanofiltered C1-Inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;363:513–22.
14 Zuraw BI, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-Inhibitor in hereditary angioedema. *Am J Med* 2012;125:938.e1–7.
15 CINRYZE (C1 inhibitor [human]) Summary of Product Characteristics. ViroPharma SPRL. Issued February 2014 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001207/WC500108895.pdf (accessed May 2014).