CASE REPORT

Successful treatment of acute hereditary angioedema attacks with self-administered icatibant in patients with venous access problems

Michaela Wiednig

Department for Environmental Dermatology and Venereology, Medical University of Graz, Graz, Austria

Correspondence to

Dr Michaela Wiednig, Michaela.Wiednig@klinikum-graz.at

SUMMARY

Hereditary angioedema is a rare and potentially fatal autosomal dominant disorder characterised by unpredictable skin, gastrointestinal tract or respiratory tract oedema. Plasma-derived C1-esterase inhibitors are effective in the prophylaxis or treatment of hereditary angioedema type I and II attacks, but must be administered intravenously. This may be problematic in patients with venous access difficulties. Icatibant, a bradykinin B₂-receptor antagonist, is administered subcutaneously. In July 2008 icatibant received approval for healthcare professional-administered treatment of hereditary angioedema attacks in adults. In 2011 it received European Medicines Agency and US Food and Drug Administration licences for patient-administered treatment of hereditary angioedema attacks. Given these approvals, and with the appropriate training, icatibant could provide the opportunity for patients to self-administer treatment. This is one of the first long-term follow-up reports of patients with hereditary angioedema using self-administered icatibant. During follow-up, icatibant remained effective and patient satisfaction was high.

icatibant was an effective and safe treatment option for acute attacks of hereditary angioedema types I and II.^{7 8} Icatibant is licensed in 39 countries for healthcare professional- or patient-administered symptomatic treatment of acute attacks of hereditary angioedema in adults aged 18 years or older with C1-INH deficiency and was approved for self-administration by the European Medicines Agency and the Food and Drug Administration in 2011.

C1-INH replacement therapy can prevent or treat a hereditary angioedema attack. This requires the administration of human plasma-derived C1-INH concentrate injected intravenously. Patients with frequent hereditary angioedema attacks need repeated intravenous injections and, if patients have poor venous access, central venous access devices may be required. We report on the successful treatment with subcutaneous icatibant of two patients with hereditary angioedema type I with frequent attacks and long-term venous access difficulties. Qualitative feedback assessing patient satisfaction is also provided. This is one of the first examples of long-term follow-up using self-administered subcutaneous icatibant.

BACKGROUND

Hereditary angioedema is a potentially fatal autosomal dominant disorder characterised by recurrent episodes of non-pruritic and non-pitting oedema, most commonly affecting the skin, gastrointestinal tract and respiratory tract.¹ Attack onset is unpredictable and episodes vary in frequency, severity and location.²

Hereditary angioedema affects between 1 in 10 000 and 1 in 50 000 people, with no clear ethnic variation.² For most patients, hereditary angioedema hinders their education and career choices and also impairs their daily activities to an extent comparable with severe asthma or Crohn's disease.³

The pathophysiology of hereditary angioedema has been linked to the deficiency (type I) or dysfunction (type II) of C1-INH, an important regulator of the contact-kinin system that controls bradykinin production.⁴ Plasma levels of bradykinin are higher in patients with hereditary angioedema than in normal controls and increase further during attacks.⁵

Icatibant is a selective bradykinin B₂-receptor antagonist that inhibits bradykinin-induced oedema formation.⁶ The results from three phase III studies demonstrated that subcutaneously administered

CASE PRESENTATION

Patient 1

A 70 kg Caucasian woman aged 35 years was diagnosed with hereditary angioedema type I at the age of 2 years. Typically, she suffered moderate-to-severe cutaneous attacks (of the face and hands), although severe abdominal attacks were occasionally reported. Her attack frequency fluctuated markedly. Before receiving subcutaneous icatibant in September 2009 she received on-demand treatment (but not prophylaxis) with intravenous C1-INH concentrate (1000 U). This was often distressing for her as her concomitant conditions (systemic lupus erythematosus, activated protein C resistance and hypothyreosis) had necessitated frequent intravenous injections and infusions since childhood, and it had sometimes taken three or more attempts to locate a suitable vein. This had culminated in a strong aversion to intravenous procedures.

Patient 2

A 67 kg Caucasian woman aged 53 years was diagnosed with hereditary angioedema type I during childhood. She suffered frequent abdominal, cutaneous (hands, feet and face) and mucosal swellings of moderate-to-severe intensity. Before receiving subcutaneous icatibant she received on-demand

To cite: Wiednig M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009320

Table 1 Treatment outcomes with icatibant

	Patient 1 (88 attacks)	Patient 2 (70 attacks)
Median time from treatment administration to first improvement of symptoms	30 min	2.5 h
Median time from treatment administration to complete resolution of symptoms	2.0 h	5.5 h
Adverse events	Mild reddening, burning and itching at the injection site Resolved without intervention within 4.0 h	Mild reddening, burning and itching at the injection site Resolved without intervention within 4.0 h

Median time to first improvement of symptoms and median time to complete resolution of symptoms were patient-assessed and measured using a 100 mm 3-symptom (skin swelling, skin pain, abdominal pain) visual analogue scale score.

treatment (but not prophylaxis) with intravenous C1-INH concentrate (1000 U). Her veins were abnormally thin and had a tendency to burst during access procedures. This sometimes resulted in haematoma and made it extremely difficult to locate a suitable vein.

Both patients were identified as candidates for acute treatment with subcutaneous icatibant.

SELF-ADMINISTRATION TRAINING

Both patients received icatibant self-administration training during an in-clinic visit in September 2009. They received a patient diary and diary supplement which comprised the following:

- ▶ Information on how to recognise an acute attack, including prodromal symptoms
- ▶ An easy-to-use step-by-step self-administration guide with pictograms depicting how and when self-administered medication should be used
- ▶ A summary of how, when and what information to record during an acute hereditary angioedema attack.

Following training, both patients treated each attack with a single injection of subcutaneous icatibant (30 mg).

OUTCOME AND FOLLOW-UP

Treatment efficacy

Between September 2009 and October 2010, patient 1 suffered 10 attacks. Her attack frequency increased markedly between

October 2010 and November 2011, with 78 attacks being reported. Over the same overall period (September 2009 to November 2011) patient 2 suffered 70 attacks, including a period in September 2010 when her attack frequency increased significantly to an average of one moderate-to-severe attack every 48 h.

Attack severity was measured using a 100 mm 3-symptom (skin swelling, skin pain and abdominal pain) composite visual analogue scale score.⁸ Icatibant treatment outcomes relating to patient-assessed initial symptom improvement and complete resolution of symptoms are shown in table 1. Both patients experienced injection site reactions comprising reddening, burning and itching. All the injection site reactions were mild and transient and resolved within 4 h without further medical intervention. No other adverse events were reported.

Patient satisfaction

Patient satisfaction with icatibant treatment was assessed approximately 1 week after treatment by an 8-question 5-point questionnaire. Both patients reported a high level of satisfaction with subcutaneous icatibant. The responses are summarised in table 2.

DISCUSSION

The time to complete resolution of an acute attack is strongly influenced by the interval between symptom onset and

Table 2 Patient satisfaction summary

Question	Patient 1 response	Patient 2 response
How sufficient was the self-administration training? (not at all sufficient, not sufficient, neither sufficient nor insufficient, sufficient, or very sufficient)	Very sufficient	Very sufficient
How convenient was it to carry icatibant around? (not at all convenient, not convenient, neither convenient nor inconvenient, convenient, or very convenient)	Very convenient	Very convenient
How difficult was it to prepare the injection site prior to self-injection? (very difficult, difficult, neither difficult nor easy, easy, or very easy)	Very easy	Very easy
How difficult was it to assemble and handle the syringe? (very difficult, difficult, neither difficult nor easy, easy, or very easy)	Very easy	Very easy
How stressful did you find the idea of self-injecting icatibant during an HAE attack? (very stressful, stressful, indifferent, not stressful, or not at all stressful)	Not at all stressful	Not at all stressful
How difficult was it to actually self-inject icatibant? (very difficult, difficult, neither difficult nor easy, easy, or very easy)	Very easy	Very easy
How satisfied were you with the way icatibant relieved your symptoms, compared to your usual treatment for an HAE attack? (not at all satisfied, not satisfied, neither satisfied nor unsatisfied, satisfied, or very satisfied)	Very satisfied	Very satisfied
To what degree did you prefer self-administration over administration in the clinic? (not at all preferable, not preferable, indifferent, preferable, or very preferable)	Indifferent (because of fear of needles)	Very preferable

Questions were graded on a 5-point scale (response options provided in parentheses). Responses were collated approximately 1 week after icatibant administration. HAE, hereditary angioedema.

institution of effective treatment.⁹ Self-treatment may help to minimise morbidity from such attacks.¹⁰

During the 2-year follow-up period the median time to first improvement of symptoms in our patients was 30 min and 2.5 h, respectively, and the median time to complete resolution of symptoms was 2.0 h and 5.5 h, respectively. In the non-laryngeal population (n=98) of the most recent phase III trial of icatibant, the For Angioedema Subcutaneous Treatment (FAST)-3 trial,⁸ the patient-assessed median time to initial symptom improvement was 0.8 h for icatibant compared with 3.5 h for placebo (p<0.001), and the median time to almost complete symptom relief was 8.0 h compared with 36.0 h for placebo (p=0.012).

In conclusion, we have demonstrated that, following appropriate in-clinic training, two patients with hereditary angioedema type I and poor venous access were successfully treated with self-administered subcutaneous icatibant over the follow-up period.

Learning points

- Hereditary angioedema attacks are unpredictable; laryngeal attacks can be life-threatening and must be treated quickly.
- Plasma-derived C1-INH is effective in the treatment of hereditary angioedema but must be administered intravenously. This can cause problems for patients with venous access difficulties.
- Icatibant, a bradykinin B₂-receptor antagonist, can be subcutaneously self-administered by patients with hereditary angioedema type I and II following in-clinic training by a healthcare professional.
- Two patients with hereditary angioedema type I with poor venous access were successfully treated with icatibant. In these two patients, self-administered icatibant remained effective during the period of observation (>2 years). Both patients considered icatibant to be very convenient and very easy to use.
- It is important to recognise why alternative treatment should be considered in adult patients with hereditary angioedema type I and II with venous access difficulties who are receiving C1-INH.

Acknowledgements The author would like to thank Dr Harald Reiter, Graz, Austria, for his help in treating these patients and Dr Friedrich Petuely, Vienna, Austria, for his help in sourcing their follow-up data.

Funding Medical writing support was provided by Steve Dawber BSc (Hons), Prime Medica Ltd, Knutsford, Cheshire, UK, and was funded by Shire Human Genetic Therapies (HGT). Responsibility for the opinions, conclusions and interpretation of data lies with the author and such perspectives do not necessarily reflect those of Shire HGT.

Competing interests None.

Contributors The author was responsible for supplying and interpreting the data and final approval of the manuscript.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Bowen T, Cicardi M, Farkas H, *et al.* 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;6:24.
- 2 Gompels MM, Lock RJ, Abinun M, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005;139:379–94.
- 3 Lumry WR, Castaldo AJ, Vernon MK, *et al.* The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc* 2010;31:407–14.
- 4 Todoric K, Craig T. Icatibant in the treatment of acute attacks of hereditary angioedema (HAE) in adults. *Clin Med Rev Vasc Health* 2011;3:91–8.
- 5 Nussberger J, Cugno M, Amstutz C, *et al.* Plasma bradykinin in angio-oedema. *Lancet* 1998;351:1693–7.
- 6 Bork K, Frank J, Grundt B, *et al.* Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 2007;119:1497–503.
- 7 Cicardi M, Banerji A, Bracho F, *et al.* Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010;363:532–41.
- 8 Lumry WR, Li HH, Levy RJ, *et al.* Randomized placebo-controlled trial of the bradykinin B₂ receptor antagonist icatibant for the treatment of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol* 2011;107:529–37.
- 9 Levi M, Choi G, Picavet C, *et al.* Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol* 2006;117:904–8.
- 10 Zuraw B. HAE therapies: past, present and future. *Allergy Asthma Clin Immunol* 2010;6:23.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow