

LETTER TO THE EDITOR

SWITCH TO ICATIBANT IN A PATIENT AFFECTED BY HEREDITARY ANGIOEDEMA WITH HIGH DISEASE ACTIVITY: A CASE REPORT

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Icatibant, an antagonist of the bradykinin B2 receptor, was approved for the treatment of acute attacks of hereditary angioedema in the EU in 2008. This paper presents the case of a 65-year-old woman affected by frequent acute attacks of hereditary angioedema who benefitted from a change of therapy to icatibant, following years of treatment with C1-inhibitor.

Hereditary angioedema (HAE) is a rare, autosomal dominant disease caused by mutations in the gene encoding C1 inhibitor (C1-INH). The resulting quantitative or functional deficiency affects the coagulation, complement and contact cascades, leading to overproduction of vasoactive inflammatory molecules (1, 2). Among these, bradykinin is a key mediator of HAE (3, 4).

Intermittent cutaneous or mucosal swellings last between 1 and 5 days if untreated. The extremities, the face, the genitals, the gastrointestinal and the respiratory tracts are commonly involved. Pharyngolaryngeal involvement is potentially life threatening because of the risk of asphyxiation (5, 6). Despite the significant morbidity and mortality associated with HAE, the disease is frequently unrecognized and misdiagnosed (5).

C1-INH replacement therapy is the first-choice treatment in Europe for acute attacks as well as for prophylaxis. Attenuated androgens are currently

the mainstay for the long term prophylaxis in HAE, however, the wide range of possible adverse effects requires careful risk/benefit evaluation. Antifibrinolytic agents, although less efficient than androgens for prophylaxis, offer a more favorable side effect profile (7, 8).

New treatments include improved C1-INH formulations and novel molecules: ecallantide (inhibitor of plasma kallikrein) and icatibant (selective antagonist of the bradykinin B2 receptor) (9-11). Icatibant was approved by the EMEA for treatment of acute attacks in adults with C1-INH deficiency (12). Unlike C1-INH replacement products, icatibant can be administered via subcutaneous injection (12). It could therefore be particularly useful at the onset of an attack.

We present the case of an adult female HAE patient with increasing disease activity who had been treated with C1-INH concentrate for a number of years. The patient was successfully switched to

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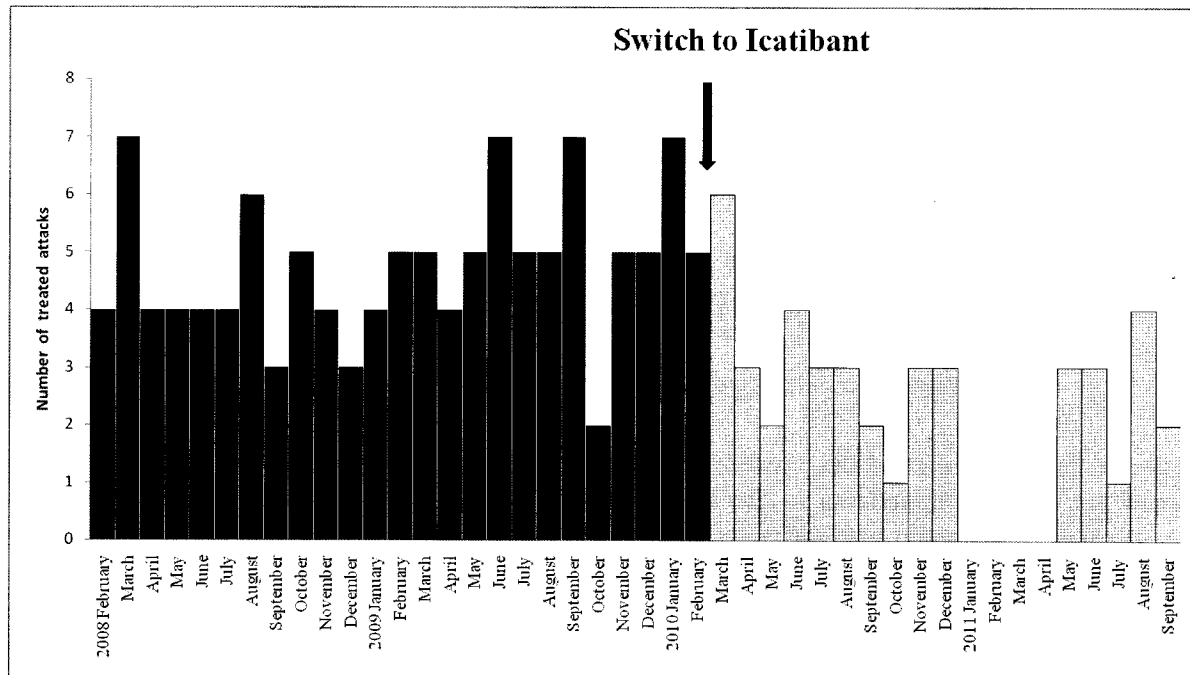


Fig. 1. Frequency of treated angioedema attacks as recorded in the patient diary, between February 2008 and September 2011. Number of treated attacks per month.

treatment with icatibant.

Case report

A 65-year-old woman, treated in our Centre since 1998, experienced an increase in the frequency of swelling attacks, particularly since 2005, despite prophylaxis and on-demand treatment. She experienced her first skin swelling at the age of 12. She then experienced recurrent vomiting, colicky pain and episodes of acute abdominal pain, misdiagnosed as irritable bowel syndrome. Episodes of laryngeal edema were rare. The patient was diagnosed with type I HAE in 1985, in her fourth decade of life, based on low C1-INH plasma levels and function and low C4-antigen. Two daughters have been diagnosed with HAE.

She then developed arterial hypertension, which was never completely controlled as beta-blockers, calcium antagonists and sartans had to be discontinued because they triggered HAE attacks. After 2004, treatment was based on doxazosin mesylate.

Following diagnosis of HAE, prophylaxis

with oral tranexamic acid (TA) was started and maintained over the years. Danazol was not tolerated due to weight gain and signs of virilization. From 1986, acute attacks were treated with human C1-INH concentrates, dosed at 20 IU/kg body weight from 1998.

In 2008, on-demand treatment with C1-INH concentrate (Berinert P, CSL Behring, PA, USA, 1000 IU per attack) for attacks of moderate to severe intensity continued to be effective in terms of symptom relief. Edema rarely persisted after treatment, but a slow increase in attack frequency was observed without evident cause, as the patient was not exposed to any known trigger. She received C1-INH treatment for acute HAE attacks 48 times in 2008, 59 times in 2009, and 12 times in the first two months of 2010.

In March 2010, the patient was given icatibant for the first time 3 hours after the onset of limb swelling and increasingly severe inspiratory dyspnea. An abdominal ultrasound scan (US) revealed an intestinal loop wall thickness of up to 7.6 mm and slight pelvic fluid collection. The patient

received a subcutaneous (sc) injection of icatibant 30 mg (Firazyr®, Shire/Jerini). During the following 15 minutes, dyspnea, nausea and abdominal pain improved, while the painful limb swelling persisted. Thirty minutes after injection, upper airway obstruction was completely resolved. After 3 hours the patient was discharged with significant symptom relief. Reversal of symptoms and limb swelling were confirmed the following day after examination. Complete resolution of the intestinal wall swelling and of fluid collection in the Douglas pouch were confirmed by ultrasound.

Based on the experience reported by the patient, total resolution of the cutaneous and abdominal attacks would have taken 36 hours with C1-INH and 72 hours without treatment. With icatibant, the reversal of respiratory symptoms was achieved in about 15 minutes, the first improvement of abdominal symptoms occurred within 1 hour, while skin symptoms were completely resolved in about 24 hours. According to the patient, the resolution of skin and abdominal symptoms was faster than with C1-INH concentrate in similar attacks.

Since starting the treatment with Icatibant (March 2010), a total of 43 attacks were treated with icatibant in a total of 19 months of follow-up (as of September 2011). Two attacks (4.65%) required a second drug injection. It is worth noting that only moderate to severe intensity attacks were treated. With the exception of a reaction at the injection site (lasting less than one hour), no treatment-related adverse events were reported. Based on the patient reports and on our records, the first 19 months of treatment appears to be associated with a clear trend towards a reduction in the number of treated angioedema attacks, switching from 4,84 treated attacks per month (Aug 2008 – Feb 2010) to 2,26 treated attacks per month (Mar 2010-Sep 2011), with a 46% reduction (Fig. 1).

Although this patient has not been tested to detect anti-C1-INH antibodies, recent data failed to demonstrate a direct relationship between circulating anti C1-INH antibodies and use of C1 inhibitor (13).

DISCUSSION

We describe a patient with severe and frequent HAE attacks no longer adequately controlled by

standard therapies. Since 2008, the patient described here had reported an average of four to five treated attacks per month, despite prophylaxis with TA and acute treatment with C1-INH concentrate. The frequency of the untreated and treated attacks (the latter shown in Fig. 1 from 2008) increased in the last decade, without known triggers. The switch to icatibant not only could bring the resolution of the attacks but, interestingly, also appears to be associated with prolonged intervals between attacks. This trend, which needs to be confirmed over longer periods, suggests that the increased attack frequency associated with long-term use of C1-INH, may be reversible.

An increasing number of attacks after many years of C1-INH therapy had been previously described by Bork and Hardt (14): though always effective, the treatment was found to be associated to a slow but continuous increase in the number of attacks in three women over the years. Bouillet et al. recently reported development of resistance to treatment with C1-INH in two patients receiving frequent concentrated infusions (15), although several aspects of this paper have been criticized (16) and need further confirmation. The mechanisms through which frequent injections of C1-INH may generate more attacks in some patients is unclear and needs to be further investigated.

To date, the efficacy of icatibant cutaneous or abdominal attacks has been evaluated in two trials comparing icatibant *versus* placebo (FAST-1 trial) and *versus* tranexamic acid (FAST-2 trial) (10). In both trials, a single dose of icatibant provided more rapid relief of symptoms than TA or placebo (10). A direct comparison between icatibant and C1-INH has not yet been carried out, but such a study would be of great interest. In our patient, icatibant provided more rapid symptom resolution compared to C1-INH. A relevant issue in HAE is the timely recognition and assessment of the disease. We found that US was useful for detecting abdominal angioedema and for following the course of the attack. We observed a correlation between the symptoms described by the patient and an objective organ alteration (edematous thickening of the intestinal wall). In agreement with other Authors (17, 18), we found US to be an easy, non-invasive, objective and reproducible method for assessing an abdominal angioedema attack and for

monitoring the response to treatment.

While we are aware that the spontaneous lifetime fluctuation of HAE attacks is a very well known phenomenon, we believe that in this single case report the observation time is long enough to affirm that this does not represent the main issue. Considering the recent approval of Plasma-Derived C1 INH in U.S., Canada and Australia (2009-2010), new data will be available to add a wider scientific background to this observation in the near future.

In conclusion, the switch from standard C1-INH therapy to icatibant in a patient with very active disease was successful, well tolerated and easily performed. The patient benefited from the switch, as a more rapid control of her treated attacks was observed as well as a reduction in the frequency of attacks. As clinical experience with icatibant and the other new HAE medications increases, more information will become available on how to further optimize HAE management.

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