



Diagnostic and therapeutic management of hereditary angioedema due to C1-inhibitor deficiency: the Italian experience

Mauro Cancian, and the Italian network for C1-INH-HAE (ITACA)

Purpose of review

Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency (C1-INH-HAE) is a rare disease, with a reported prevalence of about 1 : 50 000. C1-INH-HAE causes disabling symptoms, which may be life-threatening if swelling affects upper airways. Diagnostic procedures are now well established and the role of bradykinin as the main mediator of plasma outflow eliciting angioedema formation has been clearly elucidated.

Recent findings

Increased understanding of the pathogenesis of C1-INH-HAE allowed in recent years the development of new drugs targeted to inhibit bradykinin synthesis (Ecallantide) or activity (Icatibant). At the same time, a recombinant C1-INH concentrate (Ruconest) was produced from the milk of transgenic rabbits and two plasma-derived C1-INHs (Berinert, Cinryze) underwent controlled trials to obtain marketing authorization. In 2012, an Italian network for C1-INH-HAE (ITACA) was established by physicians of 17 HAE reference centres to collect data from Italian patients and to homogenize and improve the diagnostic and therapeutic approach to the disease.

Summary

Although there is a widespread agreement on therapeutic goals and treatment of C1-INH-HAE acute attacks, different approaches to prophylaxis are still present among HAE experts. The clinical experience of ITACA on a large population of C1-INH-HAE patients followed for several years may help in identifying the most effective strategies for the management of the disease.

Keywords

attenuated androgens, bradykinin receptor antagonist, C1-inhibitor, hereditary angioedema, prophylaxis

INTRODUCTION

Hereditary angioedema (HAE), whose clinical picture was originally described by William Osler in 1888 [1], is a rare condition transmitted in an autosomal-dominant genetic pattern as shown by Crowder and Crowder [2]. Fifty years later, it became evident that the disease might be caused by a defect in the C1 esterase inhibitor (C1-INH), either as reduced C1-INH plasma levels (C1-INH-HAE type I) or as qualitative deficiency (C1-INH-HAE type II) [3,4]. The pathogenesis of this disease was clarified thereafter with prominent role of the contact system eventually leading to bradykinin release [5–8]. More recently, a novel type of HAE with normal C1-INH (nC1-INH-HAE), not addressed in this manuscript, has been identified [9,10].

After the first report of an Italian family with C1-INH-HAE in 1973 [11], the number of diagnoses has progressively grown throughout the Country

and in 2007 a panel of experts gathered to release the first national guideline for diagnosis and treatment of C1-INH-HAE [12]. Thenceforth, Italian centres dedicated to HAE under patronage of the Italian Hereditary Angioedema Patients' Association (<http://www.angioedemaereditario.org>) convened and in 2012 established the Italian network for C1-INH-HAE (ITACA), which is now based on 17 centres [13] with homogeneous protocols and facilities to diagnose and treat patients with C1-INH-HAE.

The aim of this article was to describe the ITACA approach to C1-INH-HAE, based on results of

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KEY POINTS

- The pathogenesis of hereditary angioedema (HAE) because of C1-INH deficiency (C1-INH-HAE) has been elucidated in the past years, with particular regard to the role of bradykinin as the main mediator of the disease.
- Innovative strategies and drugs have been recently developed for the management of both acute attacks and prophylaxis of C1-INH-HAE.
- The constant sharing of data and clinical experience may help reference centres for HAE to homogenize and improve the management of the disease.

controlled trials, recent guidelines or consensus statements and long-standing, fully shared Italian clinical experience in real-life on more than 1000 patients.

PATHOPHYSIOLOGY AND DIAGNOSIS

To date, about 350 different mutations (Human Genome Mutation Database, <http://www.hgmd.cf.ac.uk/ac>) in C1-INH gene (SERPING1, OMIM #608660) have been demonstrated to cause C1-INH deficiency, but no genotype/phenotype correlation has been found so far [14–19]. C1-INH belongs to the superfamily of the serin protease inhibitors (SERPIN) and controls several proteases in the complement, coagulation, contact and

fibrinolytic systems [6,20,21,22[■]]. Uncontrolled local activation of the contact system leads to overproduction of bradykinin (BK) that binds BK-B2 receptor (BK-B2r) on endothelial cells. Stimulation of these receptors opens cell junctions allowing plasma outflow and angioedema formation [23[■]] in the deep dermis and subcutaneous or submucosal layers of the face, larynx, abdomen and extremities. C1-INH-HAE is not associated with urticarial wheals and acute attacks resolve in 1–5 days [24].

Symptoms tend to recur life-long and significantly affect patients' quality of life by limiting scholastic, working and social activities. Gastrointestinal involvement is typical of C1-INH-HAE and may help to differentiate this form from other angioedema [25[■]]. It is characterized by bowel occlusion with severe crampy pain, vomiting and diarrhoea, so closely mimicking surgical emergencies to prompt unnecessary operations [26–28] (Fig. 1). Laryngeal attacks represent roughly 5% of all symptoms and can easily be lethal in undiagnosed patients [29]. Precipitating factors for HAE attacks may include medications such as oral estrogens or angiotensin-converting enzyme inhibitors, infection, trauma, hormonal changes, and surgical, endoscopic, or dental procedures [24]. Nevertheless, in most cases angioedema occurs spontaneously and the unpredictable onset of symptoms may worsen the burden of illness [30,31[■]].

The worldwide prevalence is estimated between 1:10 000 and 1:50 000 [32–36]. Data recently

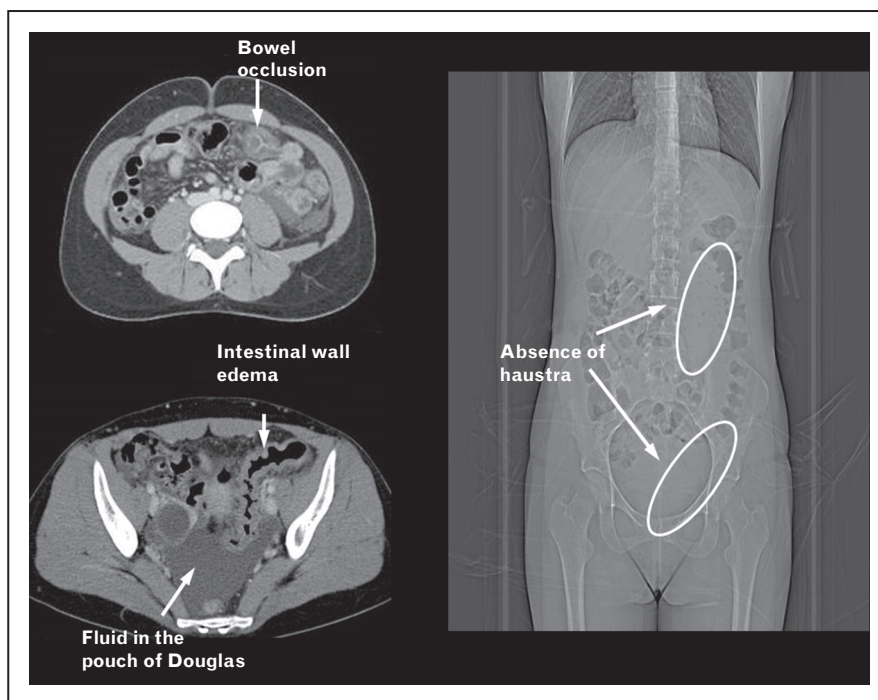


FIGURE 1. Abdominal CT-scan of an acute attack of C1-INH-HAE in a woman.

collected by the Italian network for HAE provided a prevalence of 1:64935 for our country, with no sex differences [13[■]].

Whenever a patient reports a history of recurrent, nonhistaminergic subcutaneous or upper airway angioedema and/or abdominal pain attacks of unknown etiology, C1-INH deficiency should be taken into account [25[■]]. Gastrointestinal involvement as the only symptom of the disease is rare, and the diagnosis is particularly challenging in this situation. A positive family history further strengthens the suspicion of C1-INH deficiency, but even in the absence of family history HAE needs to be considered as up to 20–25% of cases represent de-novo mutations [32,33,37].

Laboratory assay includes C4, quantitative and functional C1-INH assessment. For diagnosis of C1-INH-HAE type I both plasma C1-INH antigen and function need to be less than 50% of normal control population. In the Italian HAE cohort, this variant accounts for 87% of patients whereas in the remaining 13% only C1-INH activity is below 50% of normal (C1-INH-HAE type II) [13[■]], a finding similar to those reported in other series [4,38]. Screening with C4 plasma levels, a cheap assay available in most laboratories, may also be very helpful because values more than 50% of the reference range exclude diagnosis with 96% accuracy [13[■],38,39]. SERPING1 sequencing may be necessary when family analysis does not prove existence of genetic basis for C1-INH deficiency and for prenatal/perinatal diagnosis. In Italy, we chose to centralize C1-INH genotyping in a single referral centre to optimize costs and standardize quality of tests.

Although diagnostic criteria are well established and easy to apply, the delay between onset of symptoms, which typically present in childhood, and diagnosis of C1-INH-HAE is still substantial [30,32,33,40] and in Italy amounts to about 10 years [13[■]].

More rarely, C1-INH deficiency is caused by increased catabolism in patients with no mutation affecting the SERPING1 gene and in whom lack of a family history is constant. C1-INH-acquired angioedema (C1-INH-AAE) is usually associated with lymphoproliferative or immune diseases and commonly starts later than C1-INH-HAE, e.g. in middle or advanced age. Skin and mucosal involvement is otherwise similar to hereditary angioedema, but in addition to low levels of C4, antigen and functional C1-INH also C1q is usually reduced and anti-C1-INH autoantibodies may be detected [20,41].

THERAPY

Since the first international consensus conference on C1-INH-HAE management in 2003 [42], guidelines and position papers were regularly released to

reflect progress in therapy and results from clinical and observational studies [43–45]. The last expert panel recommendations and an extensive review on the different strategies and drugs available for C1-INH-HAE were published in 2014 [46[■],47[■]].

Acute attacks can be treated by C1-INH replacement, inhibition of plasma kallikrein or blockade at the BK-B2r (Fig. 2), whereas attenuated androgens and infusion of plasma-derived C1-INH concentrate (pd-C1-INH) may be used both for short-term and long-term prophylaxis [44,45,46[■],47[■]] (Table 1).

There is a widespread agreement on therapeutic goals (reduce mortality and morbidity; prevent recurrence of attacks; improve quality of life) as well as on the opportunity to provide all patients with at least two doses of drug available at home for treating an acute attack, to train them for self-administration and to encourage a prompt treatment of attacks [44,45,46[■]].

Nevertheless, different approaches to the time for switching from on-demand to long-term prophylaxis are present among HAE experts [44].

Acute attacks (on-demand therapy)

Three C1-INH concentrates (Berinert, Cinryze, Ruconest) and the BK-B2r antagonist Icatibant are at present licensed in Italy to treat acute attacks, whereas we have no direct experience with the kallikrein inhibitor Ecallantide [48] that is not approved in Europe. All mentioned medications were shown to be highly more effective than placebo – or tranexamic acid for Icatibant – in randomized, double-blind, placebo-controlled clinical trials. No head-to-head trials compared the relative efficacy of these drugs.

Berinert

Berinert is a plasma-derived, pasteurized and nano-filtered C1-INH concentrate [49] which is available in Italy from 2003 (a concentrate from Immuno Baxter had been previously marketed in our country between 1985 and 2003). In the past, we used to prescribe fixed doses of intravenous 500 U for peripheral and abdominal attacks – or overall in the pediatric population – and 1000 U or higher amounts for the facial and laryngeal ones [12]. Although this strategy was shown to be effective in clinical practice [50], based on the results of the IMPACT-1 and IMPACT-2 studies [51,52], Berinert is at present licensed for self-administration with a weight-based dosage of 20 U/kg in the treatment of all types of attacks in adults and children.

Cinryze

Cinryze is a heat-treated, nanofiltered C1-INH product purified from human plasma and marketed in Italy from 2013. Cinryze may be self-administered

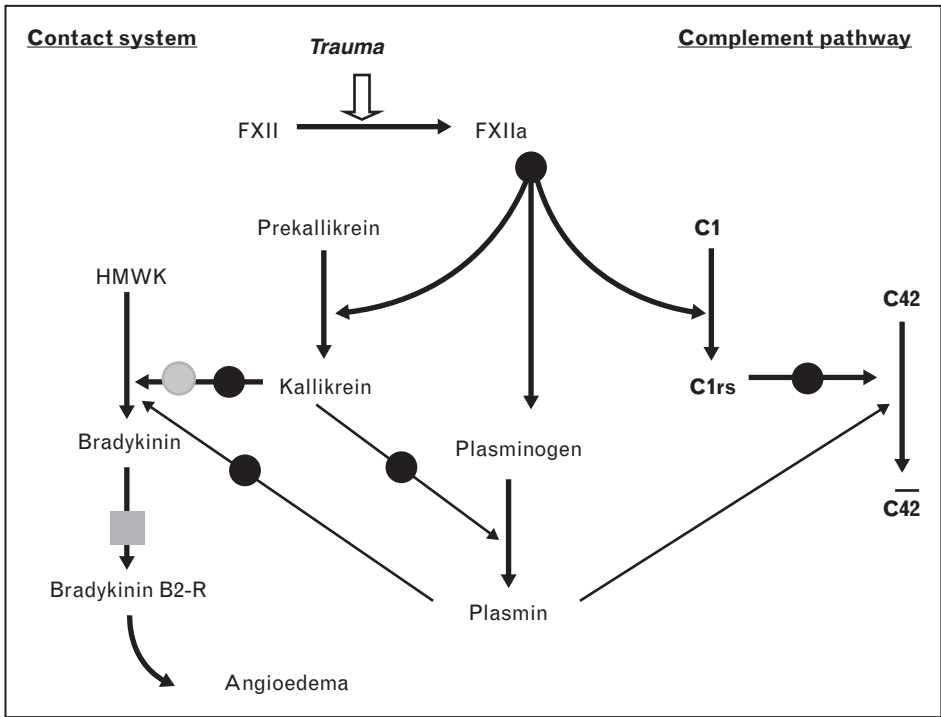


FIGURE 2. Pathophysiology of C1-INH-HAE and site of action of targeted drugs. Black circle, plasma-derived or human-recombinant C1-INH concentrate; gray circle, Ecallantide; gray square, Icatibant. HMWK, high molecular weight kininogen.

on acute episodes of HAE in adults and children as an intravenous infusion at the fixed dose of 1000 U followed by additional 1000 U if no effect is obtained after 1 h [53,54]. Given that the efficacy of C1-INH replacement seems to be dose-dependent and correlates with peak plasma levels [55], this may explain why in the acute attack-treatment clinical trial for Cinryze marketing authorization most of the participants required a second injection of the study drug [53]. Unlike Europe, Cinryze is approved for prophylaxis but not for on-demand therapy in the United States.

Ruconest

Ruconest (conestat alfa, Rhucin) is a human recombinant C1-INH (hr-C1-INH) extracted from the milk of transgenic rabbits. Two separate phase

III randomized, placebo-controlled trials were conducted in Europe (with a 100 U/Kg) and in North America (with 100 U/kg or 50 U/kg): the 50 U/kg dose proved to be effective in most acute attacks, with only around 10% of the patients needing a second infusion [56]. Thus, Ruconest is licensed (in Italy since 2012) for management of acute attacks in adults by a healthcare professional, with a posology of 50 U/kg up to 84 kg body weight and of one intravenous injection of 4200 U for heavier individuals. Rabbit sensitivity should be ruled out before drug administration.

Icatibant

Icatibant (Firazyr), a synthetic, selective BK-B2r antagonist, has been available in Italy since 2009 as prefilled syringes containing 30 mg of drug to be

Table 1. Therapeutic strategies for management of C1-INH-HAE in Europe		
On-demand therapy	Long-term prophylaxis	Short-term prophylaxis
Aim	Aim	Aim
Rapidly resolve the acute attack	Decrease the number and severity of attacks	Prevent procedure or stress related attacks
Prevent life-threatening complications	Reduce the burden of illness	Allow patients to receive medical care
Available treatments*	Available treatments	Available treatments
pd/hr C1-INH	pd C1-INH	pd C1-INH
Icatibant	Attenuated androgens	Attenuated androgens

hr, human recombinant; pd, plasma-derived.
*Kallikrein inhibitor Ecallantide is not authorized in Europe.

self-injected subcutaneously for treatment of acute attacks in C1-INH-HAE adult patients. Two parallel phase III studies, FAST-1 (in the United States) and FAST-2 (in Europe and Israel), respectively, against placebo and tranexamic acid assessed efficacy to obtain relief of symptoms in acute HAE attacks. As the endpoint was initially reached just in FAST-2, Icatibant was licensed in Europe starting from 2008 [57]. Another similar trial, FAST-3, showing Icatibant to be significantly superior to placebo was necessary for FDA approval given in 2011 [58]. Probably because of the short plasma half-life, approximately 10% of patients require a further dose for recurrence of symptoms.

All these drugs are effective for on-demand therapy, with specific limitations and potential adverse effects (Table 2). Plasma-derived products need continuous surveillance for their infectivity potential, but no case of blood-borne infection has been reported for pd-C1-INHs currently available for HAE since their presence on the market [59,60]. Thus, in the ITACA opinion the therapeutic approach should be tailored mostly by the ability of patients to self-infuse drugs and by the individual frequency of treatment effectiveness versus rebounds with different therapies. Attitude to self-administration, not yet approved for Ruconest, is particularly relevant allowing early on-demand treatment and to maintain personal safety without affecting day-to-day life [61–63]. Costs of an effective treatment are similar for the different drugs, and some patients may have alternative therapies, e.g. both a C1-INH concentrate and Icatibant, available

at home to treat different kinds of attacks with the drug that they have experienced to be more effective in a particular situation. Fresh frozen plasma, which contains not only C1-INH but also potential substrate for bradykinin generation, should only be used if targeted therapies are not available and reserved for life-threatening attacks [45,46*].

Long-term prophylaxis

In patients with frequent attacks and in whom on-demand therapy is inadequate to achieve adequate control of the disease, regular therapy to prevent episodes of angioedema should be considered. Attenuated androgens or pd-C1-INH can be prescribed in Italy for long-term prophylaxis (LTP), whereas we no longer recommend the off-label use of antifibrinolytic agents because randomized trials supporting their efficacy are lacking and clinical benefits are highly variable and limited to restricted numbers of patients. Given that angioedema attacks may even occur during routine prophylaxis, all patients must have available on-demand therapy at home.

Attenuated androgens

Attenuated androgens have been used in Italy, where danazol is licensed for treatment of hereditary angioedema, since the 1970s and was shown to be very effective in preventing C1-INH-HAE attacks [64–67]. Their use is, however, contraindicated until after puberty as well as in pregnant or breast-feeding women, and may be limited by the many potential

Table 2. Drugs currently available in Europe for specific management of C1-INH-HAE

Drug	Characteristics	Indication	Dose	Potential side-effects and limitations
Beriner	Plasma-derived C1INH concentrate	Acute treatment; short-term prophylaxis	20 U/kg body weight intravenous for acute treatment. 1000 U for STP	Theoretical transmission of blood-borne infectious agents
Cinryze	Plasma-derived C1INH concentrate	Acute treatment; short-term prophylaxis; long-term prophylaxis	1000 U intravenous for acute treatment and STP. 1000 U q3–4 days for LTP	Theoretical transmission of blood-borne infectious agents. Avoid indwelling catheters for LTP (potential risk of thrombosis)
Ruconest (Rhucin)	Human recombinant C1INH concentrate	Acute treatment	50 U/kg intravenous up to 84 kg body weight. 4200 U for heavier patients	Potential anaphylaxis (rule out rabbit allergy before administration). Not authorized under 18 years of age nor for pregnant and breast-feeding women. Self-administration not allowed
Icatibant (Firazyr)	Synthetic Bradykinin- B2 receptor antagonist	Acute treatment	30 mg subcutaneous injection	Negligible pain and swelling at injection site. Theoretical risk of exacerbating coronary heart disease. Not authorized under 18 years of age nor for pregnant and breast-feeding women

LTP, long-term prophylaxis; STP, short-term prophylaxis.

adverse effects. Weight gain, hypertension, dyslipidemia, mood disorders, acne, cholestasis and sporadic cases of hepatic adenoma have been reported in both sexes, whereas virilization, changes in libido and menstrual irregularities are among the most common side-effects in the female sex [65–70]. As adverse effects are dose-dependent, danazol intake should not exceed 200 mg per day and be adjusted to the minimal effective dose. Patients on androgen LTP must be monitored for blood pressure and screened at regular intervals by complete blood count, urine analysis, lipid panel, liver function and upper abdomen ultrasound.

Plasma-derived C1-inhibitor

Although Berinert has long been used in Europe for routine prophylactic treatment [60], Cinryze is at present the only C1-INH concentrate approved for this specific purpose [47²²]. Italian health authorities authorize LTP in HAE patients intolerant or refractory to prior danazol therapy and with need for on-demand treatment at least four times a month over 3 consecutive months. Intravenous infusion of 1000 U every 3 to 4 days was shown to reduce the number and severity of attacks in both randomized and open-label studies [53,54,71,72], but subsets of patient may require dose and/or interval adjustment to optimal control. Cinryze-associated thrombotic events, probably related to indwelling venous catheter rather than to the drug itself, have been reported during routine prophylaxis in a few patients with hereditary angioedema [73].

The first issue when considering LTP for hereditary angioedema is how to identify patients who need this approach. An effort to establish objective criteria to assess the inadequacy of on-demand therapy before shifting to routine prophylaxis did not achieve unanimous agreement [44]. LTP is usually initiated whenever on-demand treatment fails in reverting patients to a satisfactory quality of life, there are no specific contraindications and in physicians' opinion the expected benefits are more relevant than the potential risks.

The decision to use one over the other therapeutic option should be individualized and take into account data on drug efficacy and overall adverse effects, ease of use for individual persons and costs, which are significantly higher for Cinryze than for danazol. Based on scientific evidence, the above-mentioned concerns and clinical experience, the Italian network for HAE feels that danazol may still be considered the first-line long-term prophylactic treatment for adult patients responsive to low doses (50–200 mg daily), in whom androgenic effects are not perceived as relevant and having no evidence of metabolic, behavioural or hepatic complications.

Unlike the past, when LTP was usually started with high doses of androgens (e.g. danazol 600 mg daily) [12,65–69], in our experience the current posology is well tolerated by most patients and does not produce significant adverse effects as assessed by periodic monitoring. Approximately 20% of the Italian C1-INH-HAE patients are at present on LTP with danazol, and 1% with pd-C1-INH, respectively.

Short-term prophylaxis

Although most of HAE attacks occur spontaneously, it is well known that local trauma, stress and surgical procedures may trigger angioedema. Physicians and patients are frequently concerned about the risk of swelling associated with upper airway manipulation, including dental care, but even minor procedures can induce angioedema anywhere from few to many hours later. Thus, depending on the kind of procedure and on patients' history of previous HAE attacks in similar conditions, a course of short-term prophylaxis (STP) may be planned when appropriate [44,45,46²³].

The efficacy of STP with pd-C1-INH has been evaluated by retrospective studies [74,75] on dental procedure or irrespective of the type of surgery and shown to be dose-dependent. Both Berinert and Cinryze are licensed in Italy for preprocedural prophylaxis, and we suggest infusing the recommended dose of 1000 units about 1–2 h before the procedure.

Danazol may be considered an alternative to pd-C1-INH for STP, but needs to start 5 days before and continued 2–3 days after the procedure (2.5–10 mg/kg/day, maximum 600 mg/day in adults and 300 mg/day in children).

As breakthrough attacks may still occur with preprocedural prophylaxis, on-demand treatment must be always available as rescue therapy. Finally, although scientific evidence is lacking in selected cases we suggest STP also on stressful life experiences or when travelling in areas with limited health resources.

Concluding remarks

In the past 10 years innovative drugs have been licensed for the treatment of C1-INH-HAE and from application trials we learned more also about the pd-C1-INH that we had used for a long time. However, no comparative study among targeted therapies for this rare disease has been conducted so far and the numbers of patients referring to a single physician are usually small. The efforts by the Italian network for C1-INH-HAE to pool clinical data of patients and share clinical experience help to improve and homogenise the management of the disease in the real world.

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Conflicts of interest

M. Cancian has received speaker's fees from CSL Behring, SOBI and Viropharma and has served on advisory boards for CSL Behring, Pharming NV, Shire, SOBI and Viropharma. F. Arcoleo received consultancy fees and research grant funds from Shire. M. Bova has received sponsorship for educational purposes, has been paid for providing consultancy services and has taken part in clinical trials sponsored by Shire, Pharming NV, CSL Behring and SOBI. M. Cicardi received fees for consultancy and/or as invited speaker from Biocryst, CSL Behring, Dyax, Pharming NV, Shire and SOBI. P. Minale has received speaker fees from Shire. O. Rossi received editorial support from Viropharma and consultancy fees from CSL Behring and Shire. V. Montinaro received consultancy fees from CSL Behring, Shire, Viropharma and research grant funds from CSL Behring. M. Triggiani received research support from CSL Behring and consultancy fees from Shire, SOBI and Viropharma. A. Zanichelli has received speaker fees from CSL Behring, Shire, SOBI and Viropharma, and consultancy fees from CSL Behring, Shire and Viropharma. A. Zoli served as a consultant for Shire. The other authors have no conflicts of interest to disclose.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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