Clinical & Experimental Immunology
The Journal of Translational Immunology

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/cei.12910

Comparing acquired angioedema with hereditary angioedema (types I/II): findings from the Icatibant Outcome Survey

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Accepted for publication 11 November 2016
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Summary

Icatibant is used to treat acute hereditary angioedema with C1 inhibitor deficiency types I/II (C1-INH-HAE types I/II) and has shown promise in angioedema due to acquired C1 inhibitor deficiency (C1-INH-AAE). Data from the Icatibant Outcome Survey (IOS) were analysed to evaluate the effectiveness of icatibant in the treatment of patients with C1-INH-AAE and compare disease characteristics with those with C1-INH-HAE types I/II. Key medical history (including prior occurrence of attacks) was recorded upon IOS enrolment. Thereafter, data were recorded retrospectively at approximately 6-month intervals during patient follow-up visits. In the icatibant-treated population, 16 patients with C1-INH-AAE had 287 attacks and 415 patients with C1-INH-HAE types I/II had 2245 attacks. Patients with C1-INH-AAE *versus* C1-INH-HAE types I/II were more often male (69 *versus* 42%; $P = 0{\cdot}035$) and had a significantly later mean (95% confidence interval) age of symptom onset [57·9 (51·33–64·53) *versus* 14·0 (12·70–15·26) years]. Time from symptom onset to diagnosis was significantly shorter in patients with C1-INH-AAE *versus* C1-INH-HAE types I/II (mean 12·3 months *versus* 118·1 months; $P = 0{\cdot}006$). Patients with C1-INH-AAE showed a trend for higher occurrence of attacks involving the face (35 *versus* 21% of attacks; $P = 0{\cdot}064$). Overall, angioedema attacks were more severe in patients with C1-INH-HAE types I/II *versus* C1-INH-AAE (61 *versus* 40% of attacks were classified as severe to very severe; $P < 0{\cdot}001$). Median total attack duration was 5·0 h and 9·0 h for patients with C1-INH-AAE *versus* C1-INH-HAE types I/II, respectively.

Keywords: acquired angioedema, hereditary angioedema, icatibant

Introduction

Angioedema due both to acquired and hereditary C1 inhibitor (C1-INH) deficiency (C1-INH-AAE and C1-INH-HAE, respectively) [1] is associated with a lack of functional C1-INH. C1-INH-HAE type I results from reduced levels of C1-INH, while type II from dysfunction of C1-INH [2]. As with C1-INH-HAE, C1-INH-AAE has been divided traditionally into two types: I and II. Patients with C1-INH-AAE type I have a lymphoproliferative disease and over-consumption of C1-INH, whereas those with type II produce anti-C1-INH autoantibodies, usually related to monoclonal gammopathy or, less often, a lymphoid haemopathy [3,4]. However, its pathophysiology is not defined fully [5], and this division is not concrete; patients often have lymphoproliferative diseases together with autoantibodies to C1-INH [3,6].

Both C1-INH-HAE types I/II and C1-INH-AAE are rare disorders; in the general population, the estimated prevalence is approximately 1 : 50 000 and 1 : 500 000, respectively

[7,8]. Unlike HAE types I/II, C1-INH-AAE is associated with older age at onset (usually affecting patients older than 40 years) and presents typically with recurrent attacks that most commonly involve the tongue, uvula and upper airways and face, although other areas of the body can be affected. Additionally, patients with C1-INH-AAE have a negative family history for angioedema. When C1-INH-AAE is suspected, the diagnosis is confirmed if the level of C1-INH function in plasma is below 50% [7]. Conversely, C1-INH-HAE types I/II present at an earlier age, more often involve the gastrointestinal mucosa and in most cases are associated with a family history of angioedema [1,9].

There are currently no treatments licensed by regulatory authorities for the management of C1-INH-AAE-related attacks. Thus, agents approved for the treatment of C1-INH-HAE attacks, namely plasma-derived C1-INH concentrate (Berinert®; CSL Behring, Kankakee, IL, USA; Cinryze®; Shire, Lexington, MA, USA), the bradykinin B2 receptor antagonist icatibant (Firazyr®; Shire) and the kallikrein inhibitor ecallantide (Kalbitor®; Shire) have been used to treat patients with C1-INH-AAE [9–12]. Additionally, anti-fibrinolytics and occasionally androgens can reportedly be useful for long-term prevention of attacks, and curing a causal underlying disease may be an option in some patients [9]. For C1-INH-AAE associated with autoantibodies, when prophylactic treatments are insufficient, rituximab (MabThera®; Roche, Mississauga, Ontario, Canada) can be an effective option [6].

Given the limited clinical data on treatment options for these rare disorders, information gleaned from drug registries can help to gather valuable insight into the utility of medications in these patients. The Icatibant Outcome Survey (IOS) is a registry that was designed to monitor the safety and effectiveness of icatibant in the real-world setting. Although this agent is approved currently (in Europe and the United States) to treat angioedema attacks in patients with C1-INH-HAE, in countries where the appropriate regulatory approvals have been granted, any patient with a prescription for icatibant is eligible to participate in the IOS, including those who are receiving icatibant off-label for C1-INH-AAE. The aim of this analysis was to utilize findings from the IOS registry to characterize more clearly the response to icatibant treatment, as well as to evaluate the onset, delay in diagnosis and clinical presentation in patients with C1-INH-AAE compared with those with C1-INH-HAE types I/II.

Materials and methods

Study design

IOS is an ongoing, international, prospective observational study (NCT01034969) monitoring the safety and effectiveness of icatibant during real-world use. This registry was initiated in 2009 by Shire (Zug, Switzerland); by April 2015, 50 sites in 11 countries participated, including Austria, Brazil, Denmark, France, Germany, Greece, Israel, Italy, Spain, Sweden and the United Kingdom. The study design is described in detail elsewhere [13]. Briefly, physicians completed electronic forms when their patients attended routine clinic visits, approximately every 6 months. A description of each attack that occurred between clinic visits was recorded, including the anatomical site(s), severity, time of administration of icatibant injection(s) and rescue medications, the point at which symptoms were resolved and whether the drug was self-administered or delivered by a health professional. Patients evaluated the characteristics of attacks, including their severity. Additionally, key medical history-related details and information on attacks occurring during the previous year were collected when patients enrolled in the IOS. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines, and received the approval of the respective local ethics committees and/or health authorities. Written informed consent was obtained for each patient.

Analysis

This analysis included patients with a diagnosis of C1-INH-AAE or C1-INH-HAE types I/II who enrolled in the IOS to 23 April 2015. We analysed data on icatibant-treated attacks (including attacks occurring before enrolment) by reported disease type (i.e. C1-INH-AAE or C1-INH-HAE types I/II).

Exploratory outcome measures included the percentage of attacks that involved the abdomen, skin and larynx and the proportion of patients experiencing specific attack severity (classified as very mild, mild, moderate, severe or very severe). Further outcome measures included the total number of attacks that were self-treated, the percentage of attacks requiring more than one icatibant injection and the proportion of attacks treated with C1-INH concentrate as rescue medication. Several time-related assessments were also measured, including number of hours between onset of the attack and first icatibant injection, between first and second doses of icatibant, between first administration of icatibant and resolution of symptoms, between second dose of icatibant and symptom resolution and the total duration of the attack (i.e. from onset to symptom resolution). The time span of untreated attacks occurring within 12 months of enrolling in the IOS was also calculated and recorded as an average for each affected anatomical site. Additionally, we assessed the age at which angioedema symptoms began, the age at diagnosis as well as the diagnostic delay after symptom onset for these two patient groups.

A mixed-model analysis of repeated measures (PROC MIXED; SAS Institute Inc., Cary, NC, USA) was used to compare time to treatment, time to resolution and duration of attack. The Wilcoxon–Mann–Whitney test was used to

Table 1. Characteristics of symptomatic patients

	Patients (n)	Icatibant-treated attacks (n)	Male, n (%)*	Median (range) age (years) at:			Mean delay between symptom onset and diagnosis (months)‡
				IOS enrolment	Symptom onset†	Diagnosis†	
C1-INH-AAE	16	287	11 (69)	63·1(34·6–86·2)	61·0 (33·0–80·0) 95% CI = 51·33–64·53 $n = 14$	61·2 (34·0–81·8) 95% CI = 51·58–63·64 $n = 16$	12·3 $n = 14$
C1-INH-HAE types I/II	415	2245	175 (42)	38·8 (16·5–81·2)	12·0 (0·3–77·0) 95% CI = 12·70–15·26 $n = 360$	19·8 (0·0–77·3) 95% CI = 22·29–25·48 $n = 394$	118·1 $n = 355$

*$P = 0·035$. †Differences are significant, as indicated by non-overlapping 95% CIs. ‡$P = 0·006$. C1-INH-AAE = angioedema due to acquired C1 inhibitor deficiency; C1-INH-HAE types I/II = hereditary angioedema with C1 inhibitor deficiency types I/II; CI = confidence interval; IOS = Icatibant Outcome Survey.

compare means between the two patient groups (C1-INH-AAE *versus* C1-INH-HAE types I/II). The χ^2 test (level of statistical significance, $\alpha = 0·05$) was used to compare percentages between patient groups. The generalized linear model with repeated measures (PROC GLIMMIX; SAS Institute Inc.) was used to compare severity between groups.

Results

A total of 287 icatibant-treated attacks occurred in 16 patients with C1-INH-AAE and a total of 2245 icatibant-treated attacks occurred in 415 patients with C1-INH-HAE types I/II. The majority (68·8%) of patients with C1-INH-AAE were male, compared with 42·2% of patients with C1-INH-HAE types I/II ($P = 0·035$). Excluding 32 patients with C1-INH-HAE types I/II whose data were missing, the median frequency of attacks per year at baseline was nine attacks in 383 patients. For C1-INH-AAE, excluding missing data in one patient, the median frequency of attacks per year at baseline was 10·2 attacks in 15 patients.

Diagnosis of C1-INH-AAE or C1-INH-HAE types I/II

As expected, significant differences were found between the two study populations with regard to age at onset of symptoms, age at diagnosis and delay between symptom onset and diagnosis (Table 1). Patients with C1-INH-AAE displayed their first symptoms at a mean age of 57·9 years [95% confidence interval (CI) = 51·33–64·53], compared with a mean age of 13.9 years for HAE types I/II (95% CI = 12·70–15·26). After the first recorded appearance of symptoms, mean time to diagnosis was 12·3 months for patients with C1-INH-AAE ($n = 14$ with data available), compared with a mean delay of 118·1 months in patients with C1-INH-HAE types I/II ($n = 355$ with data available; $P = 0·006$).

Affected anatomical sites and severity

In both patient groups, the greatest number of attacks occurred in the abdomen, followed by the skin (Fig. 1). The abdomen was involved in 58% of attacks in patients with C1-INH-HAE types I/II and 47% of attacks in those with C1-INH-AAE ($P = 0·010$). Although attacks affecting the skin occurred at a similar rate in both patient groups (41%), we found a trend for a higher likelihood of attacks involving the face in patients with C1-INH-AAE [34·8% ($n = 40$)] *versus* those with C1-INH-HAE types I/II [20·9% ($n = 189$; $P = 0·064$]). Notably, patients with C1-INH-AAE experienced significantly fewer severe or very severe attacks (Fig. 2) than patients with C1-INH-HAE types I/II (40 *versus* 61%, respectively; $P < 0·001$).

Treatment with icatibant

For both patient groups, most icatibant injections were self-administered (for 80% of C1-INH-AAE– and 82% of C1-INH-HAE types I/II-related attacks). Findings revealed a trend for a shorter median time between start of an angioedema attack and the first injection of icatibant in patients with C1-INH-AAE *versus* those with C1-INH-HAE types I/II [0·8 *versus* 1·5 h, respectively; $P = 0·083$;

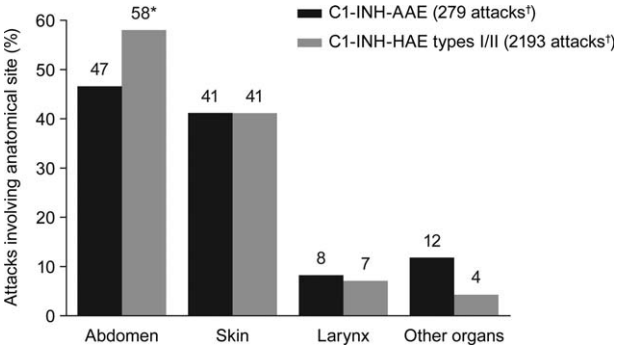

Fig. 1. Anatomical sites of angioedema attacks for C1-INH-AAE and C1-INH-HAE types I/II. Some patients experienced attacks at multiple locations, which is why totals may equal >100%. *$P = 0·010$. †Data missing for 60 attacks. C1-INH-AAE = angioedema due to acquired C1 inhibitor deficiency; C1-INH-HAE types I/II = hereditary angioedema with C1 inhibitor deficiency types I/II.

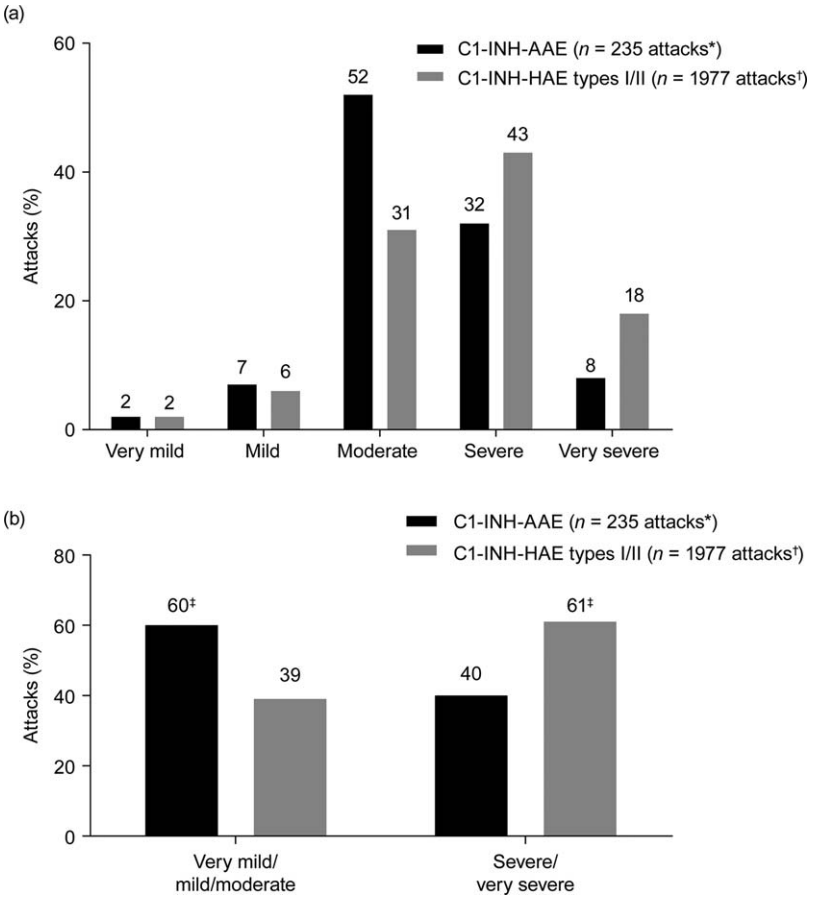

Fig. 2. (a) Severity of angioedema attacks for C1-INH-AAE and C1-INH-HAE types I/II. Attacks were categorized as very mild, mild, moderate, severe, very severe or unknown severity. (b) Summary of (a), showing severity of angioedema attacks divided into two categories: very mild to moderate, and severe to very severe. *Data missing for 45 attacks; data unknown for seven attacks. †Data missing for 191 attacks; data unknown for 77 attacks. ‡$P < 0{\cdot}001$. C1-INH-AAE = angioedema due to acquired C1 inhibitor deficiency; C1-INH-HAE types I/II = hereditary angioedema with C1 inhibitor deficiency types I/II.

Fig. 3 (corresponding to a mean time of 157·5 *versus* 254·4 min, respectively)]. Both the median time to resolution of symptoms after the first icatibant injection (2·3 *versus* 6·0 h, respectively; $P = 0{\cdot}031$) and the median total duration of attacks (5·0 *versus* 9·0 h, respectively; $P = 0{\cdot}014$) were significantly shorter in patients with C1-INH-AAE *versus* those with C1-INH-HAE types I/II (Fig. 3).

In patients with C1-INH-AAE, 5% (14 of 276) of attacks required reinjection, compared with 10% (205 of 2156) of attacks in patients with C1-INH-HAE types I/II ($P = 0{\cdot}415$). In two attacks affecting two patients with C1-INH-AAE, 26·8 and 45 h elapsed between the first and second injections. In 125 attacks affecting 52 patients with C1-INH-HAE types I/II, a median of 12·0 h elapsed between the first and second injections (interquartile range = 7·5–18·8 h).

In patients requiring a second injection, the median for symptoms to resolve, as quantified from the second injection, was 5·5 h for two attacks in two patients with C1-INH-AAE, compared with a median of 3·6 h for 96 attacks in 38 patients with C1-INH-HAE types I/II (interquartile range = 0·5–13·5 h).

C1-INH concentrate was administered as a rescue medication in 30 of 287 (10·5%) attacks in five (31·3%) patients with C1-INH-AAE and in 205 of 2245 (9·1%) attacks in 65 (15·7%) patients with C1-INH-HAE types I/II ($P = 0{\cdot}263$ for attacks and $P = 0{\cdot}097$ for patients).

Prodromal symptoms

In the C1-INH-HAE types I/II icatibant-treated population, 123 patients experienced prodromal symptoms during treated attacks ($n = 516$), including erythema marginatum (24·4%), nausea (18·7%), irritability (15·4%), tiredness (13·8%), tight or prickling sensation in the skin (10·6%), aggressiveness (4·1%) and hunger (2·4%). In the

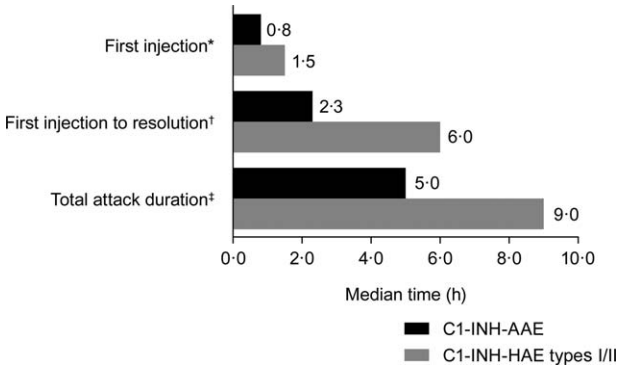

Fig. 3. Median times to first injection of icatibant and resolution of symptoms. Number of attacks: C1-INH-AAE, $n = 73$; C1-INH-HAE types I/II, $n = 830$. *$P = 0{\cdot}083$. †$P = 0{\cdot}031$. ‡$P = 0{\cdot}014$. C1-INH-AAE = angioedema due to acquired C1 inhibitor deficiency; C1-INH-HAE types I/II = hereditary angioedema with C1 inhibitor deficiency types I/II.

C1-INH-AAE icatibant-treated population, four patients (during 43 icatibant-treated attacks) experienced prodromal symptoms: one patient (6·3%) reported tiredness and three patients (18·8%) reported 'other' symptoms [during 16 attacks, such as fatigue (31·3%), cold and malaise (12·5%) and abdominal discomfort, sore throat, and painful tongue (6·3% each)]. Erythema marginatum did not appear to be a feature of C1-INH-AAE.

Duration of untreated attacks

Untreated attacks involving the abdomen, skin or larynx that occurred in the 12 months preceding a patient's enrolment in IOS were recorded retrospectively. Whereas the median duration of untreated attacks was similar for patients with C1-INH-AAE *versus* C1-INH-HAE, respectively, for attacks involving the abdomen [48·0 h; 95% CI = 10·0–72·0 ($n = 9$) *versus* 48·0 h; 95% CI = 48·0–60·0 ($n = 131$)] and skin [42·0 h; 95% CI = 24·0–72·0 ($n = 8$) *versus* 48·0 h; 95% CI = 48·0–60·0 ($n = 183$)], those affecting the larynx were shorter for patients with C1-INH-HAE [24·0 h; 95% CI = 16·0–60·0 ($n = 24$)] *versus* those with C1-INH-AAE [48·0 h; 95% CI = 8·0–72·0 ($n = 3$)].

Discussion

Observational data from the IOS support previous findings of a later age at onset and marginally less frequent abdominal involvement in patients with C1-INH-AAE compared with those with C1-INH-HAE types I/II [7], although abdominal attacks remained a frequent event in this group. Our data reported here also show a trend for attacks involving the face, consistent with previous reports that facial attacks are more common in patients with C1-INH-AAE than in those with C1-INH-HAE [7].

The majority of patients with C1-INH-AAE were male (69%; male to female ratio, 2·2), whereas patients with symptomatic C1-INH-HAE types I/II were predominantly female (58%; male to female ratio, 0·7). However, Mansi *et al.* [14] reported a similar male to female ratio in patients with symptomatic C1-INH-HAE (0·75 in 353 patients) as in those with C1-INH-AAE (0·58 in 49 patients) [14]. This discrepancy may be due to the relatively small number of patients with C1-INH-AAE enrolled in the IOS. Further studies are needed to establish whether there is an overall predominance of C1-INH-AAE in males.

Diagnostic delays in patients with C1-INH-HAE are presumed to occur because of a failure to distinguish this condition from other causes of angioedema or other acute conditions [15]. It remains unclear why patients with C1-INH-AAE in this study had a significantly shorter time between first onset of symptoms and diagnosis than those with C1-INH-HAE, but it may relate to the acceptance of symptoms in families with HAE that most patients would find unacceptable, or perhaps it relates to its association with other diseases, leading patients to seek medical attention.

In patients with C1-INH-AAE, duration of icatibant-treated attacks was shorter and a smaller proportion of attacks required reinjection compared with patients with C1-INH-HAE types I/II, which was possibly related to a quicker time to injection and/or to the milder attack severity. However, it is also possible that icatibant is more effective in this group of patients with increased consumption, rather than in patients with a genetic C1-INH deficiency.

Unlike the case with treated attacks, the duration of untreated attacks involving the skin and abdomen that occurred within 12 months before enrolment in the IOS was not shorter in patients with C1-INH-AAE than in those with C1-INH-HAE types I/II, further emphasizing the possibility that icatibant is a more effective treatment in patients with C1-INH-AAE.

Key limitations of this analysis include the fact that some data were missing due to incomplete descriptions of attacks, and there was a lack of controlled conditions in this observational retrospective study; statistical testing was considered exploratory. Also, patients with C1-INH-AAE were evaluated against patients within a different age group and with slightly different characteristics of angioedema attacks. Additionally, there were only 16 patients with C1-INH-AAE compared with 415 patients with C1-INH-HAE types I/II. Finally, the retrospective documentation of attacks may have reduced the accuracy of the results. Ideally, patients with C1-INH-AAE would be evaluated in a controlled study. However, given the rarity of this disease, conducting such a study is challenging and speaks to the general difficulties in identifying large enough patient samples to conduct clinical trials for rare diseases. From this perspective, the collection of real-world data from drug registries provides valuable insight that helps to support clinical trial data while assessing real-life product use and treatment patterns, thus increasing our understanding of the natural history and epidemiology of rare diseases. Hence, findings such as those reported here may help improve understanding of the nature of angioedema attacks, patient demography and the utility of treatment for patients with C1-INH-HAE and C1-INH-AAE.

Acknowledgements

This research was funded by Shire Development, LLC. Under the direction of the authors, Clare Guni BMBS, Sally Hassan PhD and Sophia Shumyatsky PharmD, employees of Excel Scientific Solutions, provided writing assistance for this publication. Editorial assistance in formatting, proofreading, copy-editing and fact checking was also provided by Excel Scientific Solutions. Shire Development, LLC provided funding to Excel Scientific Solutions for support in writing and editing this manuscript. The interpretation of the data, and the decision to submit the manuscript for

publication in *Clinical and Experimental Immunology*, was made independently by the authors. The authors would like to thank the IOS investigators for their contributions: Austria: W. Aberer; Brazil: A. S. Grumach; Denmark: A. Bygum; France: C. Blanchard Delaunay, L. Bouillet, B. Coppere, O. Fain, S. Guez, P. Jeandel, G. Kanny, D. Launay, L. Martin, A. Masseau, Y. Ollivier, C. Dzviga, A. Gompel, B. Goichot, H. Maillard, A. Sobel, A. Du Thanh, I. Boccon-Gibod; Germany: M. Baş, K. Bork, J. Greve, M. Maurer, E. Aygören-Pürsün, M. Bauer, I. Martinez-Saguer, U. Strassen, M. Magerl; Greece: E. Papadopoulou-Alataki, F. Psarros; Israel: Y. Graif, E. Toubi, A. Reshef, S. Kivity; Italy: F. Arcoleo, M. Cicardi, V. Montinaro, M. Triggiani, A. Zanichelli, G. Marone, P. Manconi, M. Bova; Spain: M. L. Baeza, T. Caballero, R. Cabañas, M. Guilarte, D. Hernandez, R. Lleonart, T. Lobera, L. Marques; C. Hernando de Larramendi, B. Saenz de San Pedro, G. Gala Ortiz; Sweden: J. Björkander; UK: H. J. Longhurst, C. Bethune, T. Garcez.

Author contributions

H. J. L., A. Z., T. C., L. B., M. M., O. F. and I. A. contributed to study conception and design; data acquisition, analysis and interpretation; drafting of the manuscript and critical content revisions, and final approval of content. A. W. contributed to data acquisition, analysis and interpretation; drafting of the manuscript and critical content revisions; and final approval of content. V. F. contributed to the study conception and design; analysis and interpretation; drafting of the manuscript and critical content revisions and final approval of content.

Disclosure

H. J. L. has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, Dyax, Shire and Sobi. A. Z. has received speaker fees from CSL Behring, Shire and Sobi; consultancy fees from CSL Behring and Shire; and has acted on medical/advisory boards for CSL Behring and Shire. T. C. has received speaker fees from CSL Behring, GlaxoSmithKline, MSD, Novartis and Shire; consultancy fees from CSL Behring, Novartis, Shire and Sobi; funding for travel and meeting attendance from CSL Behring, Novartis and Shire; and has participated in clinical trials/registries for CSL Behring, Dyax, Novartis, Pharming and Shire. She also is currently receiving a research grant from the IdiPaz programme to promote research activities. L. B. has received honoraria from CSL Behring, Pharming and Shire; and her institute has received research funding from CSL Behring and Shire. W. A. has acted as a medical adviser and speaker for BioCryst, CSL Behring, Pharming and Shire; and has received funding to attend conferences/educational events and donations to his departmental fund from and participated in clinical trials for Shire. M. M. has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, Dyax and Shire/Jerini AG. O. F. has provided scientific consultation for CSL Behring and Shire. V. F. was an employee of Shire at time of this analysis. I. A. is a full-time employee of Shire, Zug, Switzerland.

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