Icatibant Outcome Survey in Patients with Hereditary Angioedema: Experience in Israel Compared with Other Countries

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ABSTRACT: Background: Management of patients with hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) is evolving worldwide. Evaluating the Israeli experience may provide valuable insights.

Objectives: To compare demographics and icatibant treatment patterns and outcomes in patients with C1-INH-HAE enrolled in the Icatibant Outcome Survey (IOS) in Israel with those in other countries.

Methods: The IOS is an ongoing observational study that prospectively monitors real-world icatibant safety/tolerability and treatment outcomes.

Results: By July 2016, 58 patients from Israel and 594 patients from other countries were enrolled. Median age at diagnosis (16.7 vs. 21.3 years, P = 0.036) and median delay between symptom onset and diagnosis (0.8 vs. 6.6 years, P = 0.025) were lower in Israel compared with other countries, respectively. Differences in attack severity were not significant (P = 0.156); however, during follow-up, Israeli patients were less likely to miss > 7 days of work/school due to C1-INH-HAE-related complications (P = 0.007). A trend was also shown in Israel for earlier time to treatment (median 0.5 vs. 1.3 hours, P = 0.076), attack duration was shorter (median 5.0 vs. 9.0 hours, P = 0.026), and patients more often self-administered icatibant (97.2% vs. 87.5%, P = 0.003), respectively. However, Israeli patients were less likely to treat attacks (P = 0.036). Whereas patients in Israel reported exclusive use of danazol for long-term prophylaxis, those in other countries used various agents, including C1-INH.

Conclusions: Recognition of C1-INH-HAE and timeliness of icatibant treatment appear more favorable, and attack duration shorter, in Israel compared with other countries.

KEY WORDS: hereditary angioedema, C1-inhibitor deficiency (C1-INH-HAE), icatibant, Israel, IOS, Icatibant Outcome Survey (IOS)

ORIGINAL ARTICLES

Hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) is a rare and potentially life-threatening autosomal dominant disease caused by mutations of the SERPING-1 gene [1]. C1-INH-HAE manifests as bradykinin-mediated recurrent episodes of nonpruritic swelling of submucosal or subcutaneous tissues, often involving the limbs, genitals, face, gastrointestinal tract, and upper airways. Attacks affecting the larynx can result in asphyxiation and are life-threatening [2]. Swelling episodes occur with unpredictable frequency and severity throughout a patient’s life, contributing to a heavy burden of illness, including poor health-related quality of life and missed days of work or school [3].

Research advancements over the past decade have helped to broaden the understanding of the underlying pathophysiology and clinical manifestations of C1-INH-HAE, culminating in a progressively expanding armamentarium of treatment options and heightened disease awareness worldwide. Region-specific epidemiology, burden of illness, diagnostic challenges, and treatment patterns are increasingly being reported. HAE-focused treatment centers continue to be established throughout the world [4,5] and several international treatment guidelines have now been published [6-8]. Despite this progress, however, many obstacles remain. The rarity of this disease and the nonspecific nature of symptoms, coupled with the widely varying frequency and severity of attacks, make timely diagnosis and proactive management a continuing challenge. There is a need for enhanced awareness, education, and worldwide clinical experience with C1-INH-HAE treatment options.

Icatibant (Firazyr®, Shire, Lexington, MA, USA) is a subcutaneously administered bradykinin-B2 receptor antagonist currently licensed for acute treatment of adults with C1-INH-HAE [9]. In Europe, its label has recently been extended to include use in adolescents and children older than 2 years of age [10]. Efficacy and safety of icatibant have been demon-
strated in several phase 3 studies, including three randomized, double-blind clinical trials with open-label extensions [11–15], as well as in a prospective, open-label study evaluating self-administration [16]. Icatibant is among the key recommended treatment options for the management of acute C1-INH-HAE attacks [6].

The Icatibant Outcome Survey (IOS) is an ongoing international observational study (NCT01034969) initiated in 2009 (by Shire, Zug, Switzerland) to prospectively monitor real-world safety/tolerability and clinical outcomes with icatibant. As of 30 November 2017, 1179 patients were enrolled from 57 sites in 13 countries. Cross-country comparisons of the HAE experience provide valuable insight and help fulfill the continuing need for enhanced awareness and education worldwide.

Israel is located in the Mediterranean region and comprises approximately 8.75 million people, mostly immigrants from neighboring areas, including Africa, America, Asia, and Europe [17]. A survey of patients with C1-INH-HAE in Israel reported the presence of approximately 230 physician-diagnosed patients with this disease, most of whom are treated by academic center-based allergists and immunologists [17]. Within Israel’s National Health Insurance framework (which enables universal access to a basket of public healthcare services), Israel adopted a special program for rare-disease medications, the Extended Health Basket (EHB). Icatibant was approved in 2010 by the EHB committee for inclusion in the list of government-subsidized medications and treatments [18,19], allowing HAE specialists to prescribe this agent to patients for whom such treatment would otherwise be unaffordable.

The purpose of the current analysis was to compare demographics and icatibant treatment patterns and outcomes in patients with C1-INH-HAE enrolled in the IOS registry in Israel with those enrolled in other countries.

**Patients and Methods**

The IOS was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Approval was granted by local ethics committees and health authorities. All patients (or their legal representatives) provided informed consent.

The study is registered under ClinicalTrials.gov, study number: NCT01034969

**Patients**

As of July 2016, 58 patients with C1-INH-HAE type I/II were enrolled in the IOS at four study sites in Israel, representing 6% of the total IOS enrollment worldwide. Participating study sites included the Sourasky Medical Center, Bnai Zion Medical Center, Sheba Medical Center, and Rabin Medical Center. These patients were compared to a total of 594 patients with HAE type I/II who were enrolled in the IOS from other countries, including Austria, Brazil, Denmark, France, Germany, Greece, Italy, Spain, Sweden, and the United Kingdom.

Enrollment was open to all patients who were receiving or were candidates for treatment with subcutaneous icatibant, including those with either C1-INH-HAE type I (low plasma levels and low functional C1-INH activity) or C1-INH-HAE type II (normal/elevated plasma levels but low functional C1-INH activity) [20].

**Data Collection**

The current analysis is based on data collected from July 2009 through July 2016, at which time 966 patients were enrolled at 51 sites in 11 countries, of whom 652 were classified as C1-INH-HAE type I/II.

**Patient Visits**

Medical history was collected for each patient at the time of enrollment, including characteristics and frequency of previous attacks, and treatment history. Routine follow-up was conducted after enrollment (approximately every 6 months), at which time physicians documented key clinical information via electronic forms, including frequency of attacks since the previous visit and use of icatibant for acute treatment. For assessments relating to the follow-up period, “follow-up” refers to any time after enrollment in the IOS. The duration of the follow-up period was not quantified because it differs from patient to patient.

**Analyses**

Multiple baseline demographic parameters were captured, including gender, age at enrollment, age at which symptoms initially appeared, and delay between symptom onset and diagnosis. Other aspects assessed included frequency of hospitalizations, time missed from work or school as a result of attacks, and attack severity (very mild, mild, moderate, severe, or very severe). Time-related assessments included time from the start of an attack to the first icatibant injection, time from the first icatibant injection to complete resolution of symptoms, and total duration of attack (time from start of attack to complete symptom resolution). Various additional assessments were captured, including the number of treated versus untreated attacks, and self-administration of icatibant compared with administration by a healthcare professional.

**Statistical Analyses**

In this analysis, the chi-square test was used to compare dichotomous demographic parameters, whereas a generalized linear model for repeated measures was used to compare attack severity. Time-to-event data (time to treatment, attack duration, time to resolution) were evaluated using a mixed model or a generalized linear model for repeated measures. Level of statistical significance was $\alpha = 0.05$. 
RESULTS

DELAY IN DIAGNOSIS

The median age at diagnosis was lower (16.7 vs. 21.3 years, \( P = 0.036 \)), and median delay between onset of symptoms and definite diagnosis was shorter (0.8 vs. 6.6 years, \( P = 0.025 \)), in patients from Israel than from other IOS countries, respectively. Nearly half (47.1%) of the patients from Israel were diagnosed within 1 year of symptom onset, compared with 21.7% of patients from other countries (\( P < 0.001 \)).

The percentage of male patients (48.3% vs. 39.7%), median age at enrollment (39.2 vs. 39.4 years), and median age at symptom onset (12.0 vs. 13.0 years) were similar for patients in Israel compared with other countries, respectively [Table 1].

IMPACT OF HAE ON WORK OR SCHOOL

Whereas Israeli patients showed a trend for higher likelihood than patients in other countries to miss more than 7 days from work or school due to C1-INH-HAE-related complications before study entry (38.5% vs. 19.6%, respectively, \( P = 0.072 \)), they were less likely to do so during the follow-up period (8.7% vs. 16.6%, respectively, \( P = 0.007 \)).

TIME TO TREATMENT, ATTACK DURATION, AND TIME TO ATTACK RESOLUTION

A trend for shorter median time to treatment of attacks was shown for Israeli patients compared with other IOS countries (0.5 vs. 1.3 hours, respectively, \( P = 0.076 \)) [Table 3]. When evaluated per individual time intervals, a higher percentage of attacks were treated earlier in Israel (\( P = 0.0006 \)) [Figure 1A]. For example, 72.0% of attacks in Israeli patients were treated within 1 hour of onset, compared with 49.3% of attacks in other countries.

The duration of treated attacks was significantly shorter in Israeli patients, both for median values (5.0 vs. 9.0 hours, respectively, \( P = 0.0026 \)) [Table 3] and individual time intervals (\( P = 0.028 \)) [Figure 1B]. Fewer attacks lasted more than 5 hours in Israeli patients compared to those from other countries.

A trend was observed for shorter median time to resolution of attacks in Israel compared with other countries (4.0 vs. 6.0 hours, respectively, \( P = 0.070 \)) [Table 3], but differences for individual time intervals were not significant (\( P = 0.103 \)) [Figure 1C].

ATTACK SEVERITY, RATE OF HOSPITALIZATION,
SELF-ADMINISTRATION, AND TREATMENT OF ACUTE ATTACKS

Severity of symptoms during HAE attacks was similar in Israeli patients compared with patients in other IOS countries (very mild/mild/moderate vs. severe/very severe, \( P = 0.156 \)), and most patients did not have C1-INH-HAE-related hospitalizations in the 12 months before IOS entry (94.4% vs. 84.8%, respectively), nor during the follow-up period (95.0% vs. 88.8%, respectively). However, more patients in Israel than in other countries self-administered icatibant (97.2% vs. 87.5%, respectively, \( P = 0.003 \)), and Israeli patients were less likely to treat acute attacks [Table 2].

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Israel (n=596)</th>
<th>Other countries* (n=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (48.3)</td>
<td>236 (39.7)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (51.7)</td>
<td>368 (60.3)</td>
</tr>
<tr>
<td>Age at enrollment, years</td>
<td>58 (3)</td>
<td>594 (3)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>39.2 (29.9, 48.7)</td>
<td>38.4 (28.2, 51.8)</td>
</tr>
<tr>
<td>Min, max</td>
<td>20, 73</td>
<td>3, 82</td>
</tr>
<tr>
<td>Age at symptom onset, years</td>
<td>51 (7)</td>
<td>504 (90)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>12.0 (6.0, 19.0)</td>
<td>13.0 (5.0, 18.0)</td>
</tr>
<tr>
<td>Min, max</td>
<td>1, 60</td>
<td>0, 72</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>54 (4)</td>
<td>551 (43)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>10.7 (10.4, 28.5)</td>
<td>21.3 (13.4, 34.0)</td>
</tr>
<tr>
<td>Min, max</td>
<td>0, 70</td>
<td>0, 77</td>
</tr>
</tbody>
</table>

*Other countries include Austria, Brazil, Denmark, France, Germany, Greece, Italy, Spain, Sweden, and the United Kingdom

\( P = 0.036 \)

\( P = 0.025 \)

\( P < 0.001 \)

C1-INH-HAE = hereditary angioedema with C1-esterase inhibitor deficiency, max = maximum, min = minimum, Q = quartile

Table 2. Treatment with icatibant

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Israel</th>
<th>Other countries*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of icatibant-treated attacks per patient from 12 months before IOS entry through 11 July 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, max</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>1.0, 5.0</td>
<td>1.0, 8.0</td>
</tr>
<tr>
<td>Number of untreated attacks* per patient in the 12 months before IOS entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, max</td>
<td>5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>0, 150</td>
<td>0, 60</td>
</tr>
<tr>
<td>Number of untreated attacks in the follow-up period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, max</td>
<td>5.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>0, 9.0</td>
<td>0, 8.0</td>
</tr>
</tbody>
</table>

*Other countries include Austria, Brazil, Denmark, France, Germany, Greece, Italy, Spain, Sweden, and the United Kingdom

\( P = 0.049 \)

\( P = 0.001 \)

\( P = 0.036 \)

IOS = Icatibant Outcome Survey, max = maximum, min = minimum, Q = quartile

229
Table 3. Time to treatment, attack duration, and time to attack resolution*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Israel (n=58)</th>
<th>Other countries1 (n=594)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of attacks (missing)</td>
<td>75 (0)</td>
<td>1267 (0)</td>
</tr>
<tr>
<td>Time to treatment, hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>5.0 (0.1, 1.5)</td>
<td>1.3 (0.5, 4.0)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 48</td>
<td>0, 66</td>
</tr>
<tr>
<td>P-value*</td>
<td></td>
<td>0.076</td>
</tr>
<tr>
<td>Attack duration, hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>5.0 (2.0, 12.5)</td>
<td>9.0 (4.0, 20.5)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 67</td>
<td>0, 154</td>
</tr>
<tr>
<td>P-value*</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Time to resolution, hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>4.0 (1.5, 9.4)</td>
<td>6.0 (2.5, 14.8)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 60</td>
<td>0, 153</td>
</tr>
<tr>
<td>P-value*</td>
<td></td>
<td>0.070</td>
</tr>
</tbody>
</table>

*In patients with available information for attack duration, time to resolution, and time to treatment
1Other countries include Austria, Brazil, Denmark, France, Germany, Greece, Italy, Spain, Sweden, and the United Kingdom
2Using a mixed model for repeated measures comparing Israel with other countries

Max = maximum, Min = minimum, Q = quartile

PROPHYLACTIC TREATMENT

A total of 14 patients from Israel (24.1%) and 309 patients from other IOS countries (52.0%) reported use of long-term prophylaxis (LTP). Whereas all 14 patients from Israel reported the sole use of danazol, those from other countries reported use of various agents, including danazol (25.8%), C1-INH (10.9%), stanozolol (7.1%), oxandrolone (0.7%), tranexamic acid (13.6%), and other agents (4.9%).

DISCUSSION

Findings from a 2010 survey of patients enrolled in C1-INH-HAE patient organizations in 11 European countries and Israel indicated that C1-INH-HAE is often poorly recognized, under-diagnosed, and mismanaged [21]. Although disease awareness is increasing and C1-INH-HAE-focused treatment centers continue to be established, unmet needs still remain.

A key finding from the current IOS analysis was that patients with C1-INH-HAE in Israel were diagnosed earlier and had shorter delay from symptom onset to diagnosis compared with patients from other countries. This finding may reflect a higher percentage of patients in Israel who are diagnosed at academic centers, or perhaps a greater disease awareness among physicians, patients, and caregivers in Israel. Another contributing factor might be the small size of the country, leading to better sharing of medical information in the community. It should be noted, however, that delays in diagnosis in Europe have been shown to persist despite increased availability of HAE treatment guidelines [22].

The trend for Israeli patients to be more likely to miss more than 7 days from work or school due to C1-INH-HAE-related complications prior to IOS entry than during the follow-up period may reflect enhanced patient awareness and adoption of coping strategies over time (i.e., icatibant self-administration). Although the IOS is an observational study, enrollment into the registry and discussion of symptoms during follow-up sessions may have motivated patients to be more proactive in assuring timely management of symptoms.

Attack severity was similar among countries, yet median duration of attacks was shorter in Israel. This finding may reflect the fact that Israeli patients are better trained at identifying an oncoming attack and administering treatment earlier, which has previously been shown to result in shorter attack duration [23]. Indeed, a greater percentage of attacks in Israel were treated within 1 hour of onset. This finding underscores the benefits of specialized HAE treatment centers, which provide training in self-administration and focus on educating patients about the importance of timely treatment of attacks.

Figure 1. [A] Time to treatment (P = 0.006), [B] attack duration (P = 0.028), and [C] time to resolution (P = 0.103), in attacks with available information for time to treatment, attack duration, and time to resolution

P value used a mixed model for repeated measures comparing Israel with other countries
*Other countries include Austria, Brazil, Denmark, France, Germany, Greece, Italy, Spain, Sweden, and the United Kingdom
The exclusive use of danazol for LTP in Israeli patients likely reflects the fact that danazol and tranexamic acid are the only agents currently approved for LTP in Israel, with the latter primarily used in children. An additional finding was that the majority of IOS participants, from both Israel and other countries, did not report HAE-related hospitalizations in the 12 months before study entry, nor during the follow-up assessment period. This finding is reassuring given the fact that management of patients with C1-INH-HAE in emergency departments continues to be suboptimal [24]. Our findings likely reflect the growing availability worldwide of on-demand therapy, which is encouraged by HAE consensus recommendations [7]. Another encouraging finding was that the majority of patients in the IOS registry self-administered icatibant, which has been shown to improve outcomes. In a prospective United States-based multicenter study of patients with C1-INH-HAE, mean (± SD) attack duration was shorter with self-administration of icatibant compared with administration by a healthcare professional (547 ± 510 vs. 968 ± 717 minutes, respectively, \( P = 0.006 \)) [25].

These current findings add to the previously published clinical experience with C1-INH-HAE management in Israel. In 2008, Reshef and colleagues [5] shared their real-world experience with various HAE treatment regimens at the Sheba Medical Center Angioedema Center, both for on-demand treatment of acute attacks and for prophylaxis. They also described the development of an angioedema specialty center at their institution, focused on a centralized management approach [5]. Similar centers are increasingly being opened in Israel as well as worldwide. Cross-country collaboration between specialized centers of knowledge and healthcare professionals was emphasized as a critical need in the survey of European C1-INH-HAE patient organizations, with the goal of sharing knowledge and establishing a reference network across European countries [21].

The IOS has several limitations that merit consideration. It has a non-randomized, single-drug observational study design with no comparator group and an uncontrolled clinical environment. The fact that attacks were retrospectively documented during follow-up visits may have resulted in recall bias, with mild or moderate attacks possibly being underreported. Notably, this analysis may not fully represent the C1-INH-HAE population in Israel. In some centers, patients with C1-INH-HAE were enrolled in other clinical studies and were thus ineligible to participate in the IOS. In addition, the IOS only focuses on patients with C1-INH-HAE who are being treated with icatibant, while participation in the IOS. In addition, the IOS only focuses on patients with C1-INH-HAE who are being treated with icatibant, while participation in Israel. In some centers, patients with C1-INH-HAE were enrolled in other clinical studies and were thus ineligible to participate in the IOS. In addition, the IOS only focuses on patients with C1-INH-HAE who are being treated with icatibant, while those whose acute attacks are managed with other agents are not represented.

CONCLUSIONS

Findings from this IOS analysis provide a real-world view into differences in icatibant use in European countries and Israel, allowing evaluation of C1-INH-HAE demographics and management on a larger scale than is feasible with clinical trials in patients with rare diseases. C1-INH-HAE management in Israel appears to be more favorable than in other countries with regard to disease recognition and timeliness of treatment, as evidenced by a lower median age at diagnosis, shorter median delay from symptom onset to diagnosis, and shorter duration of C1-INH-HAE attacks. These differences may reflect a greater disease awareness among Israeli patients and healthcare providers, as well as greater patient access to angioedema-focused expert centers. Further evaluation in larger groups of patients is needed to confirm these data.

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References


**Capsule**

**Gender differences in healthcare utilization, end-stage renal disease, and mortality among Medicaid beneficiaries with incident lupus nephritis**

While systemic lupus erythematosus and lupus nephritis (LN) disproportionately affect females, previous studies suggest that males may experience poorer outcomes. Feldman and colleagues investigated gender differences in healthcare utilization, end-stage renal disease (ESRD), and mortality among patients with LN receiving Medicaid, U.S. public insurance for low income individuals. Of 2750 patients with incident LN, 283 (10%) were male. The mean ± standard deviation (SD) follow-up period for both genders was 3.1 ± 2.3 years. The mean ± SD age was 29.6 ± 13.9 years among females and 24.7 ± 14.1 years among males (P < 0.01). Males had fewer outpatient visits (incidence rate ratios [IRR] 0.88, 95% confidence intervals [95%CI] 0.80–0.97) and fewer emergency department visits (IRR 0.75, 95%CI 0.60–0.90). The 5 year cumulative incidence of ESRD was 22.3% in males and 21.2% in females. The 5 year cumulative incidence of death was 9.4% in males and 9.8% in females. Comparing males to females, there were no gender differences in ESRD (subdistribution hazard ratio [HR] 0.95, 95%CI 0.76–1.45) or death (HR 0.81, 95%CI 0.47–1.35). In this cohort of patients with incident LN, ESRD, and mortality were extremely high overall but were not increased among males compared to females. In this vulnerable population, biological and healthcare utilization differences by gender may not significantly affect outcomes.

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Eitan Israeli

“Whenever you commend, add your reasons for doing so; it is this which distinguishes the approbation of a man of sense from the flattery of sycophants and admiration of fools”

Sir Richard Steele, (1672-1729), Irish writer, playwright, and politician